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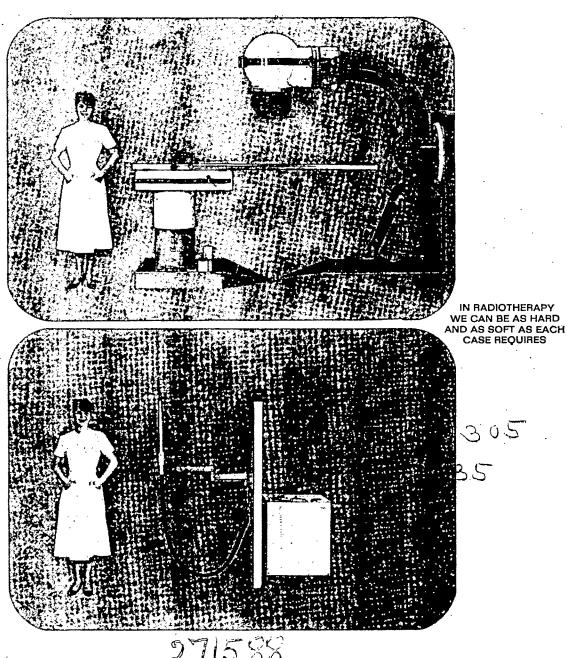
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*Margulis, A. R., and Heinbecker, P.: Am. J. Roentgenol. 86:103 (July) 1961.

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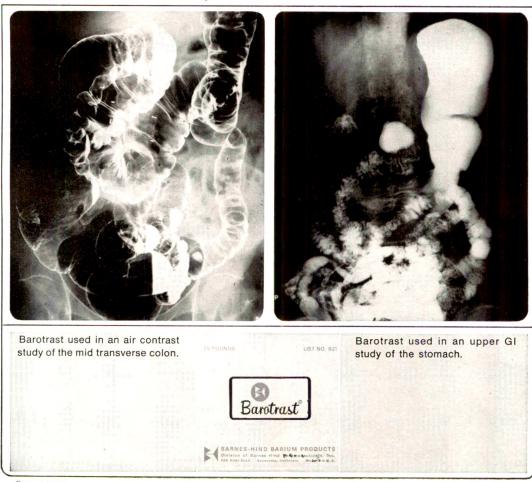
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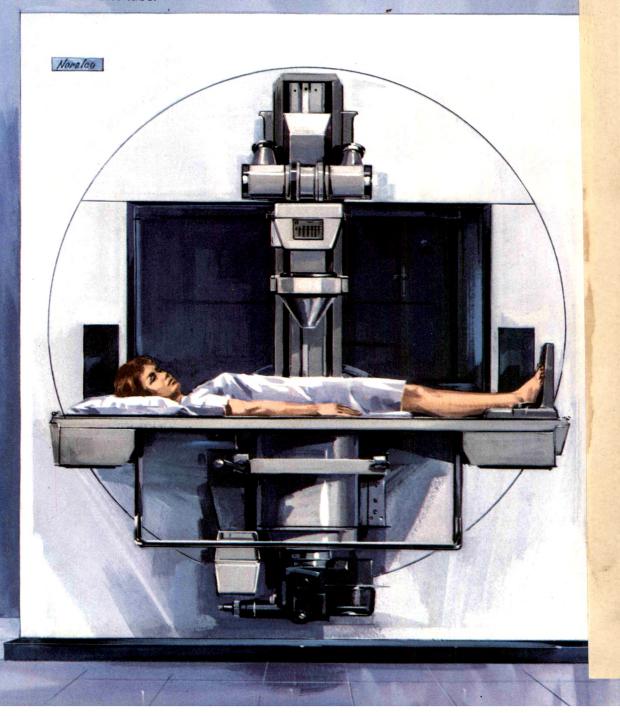
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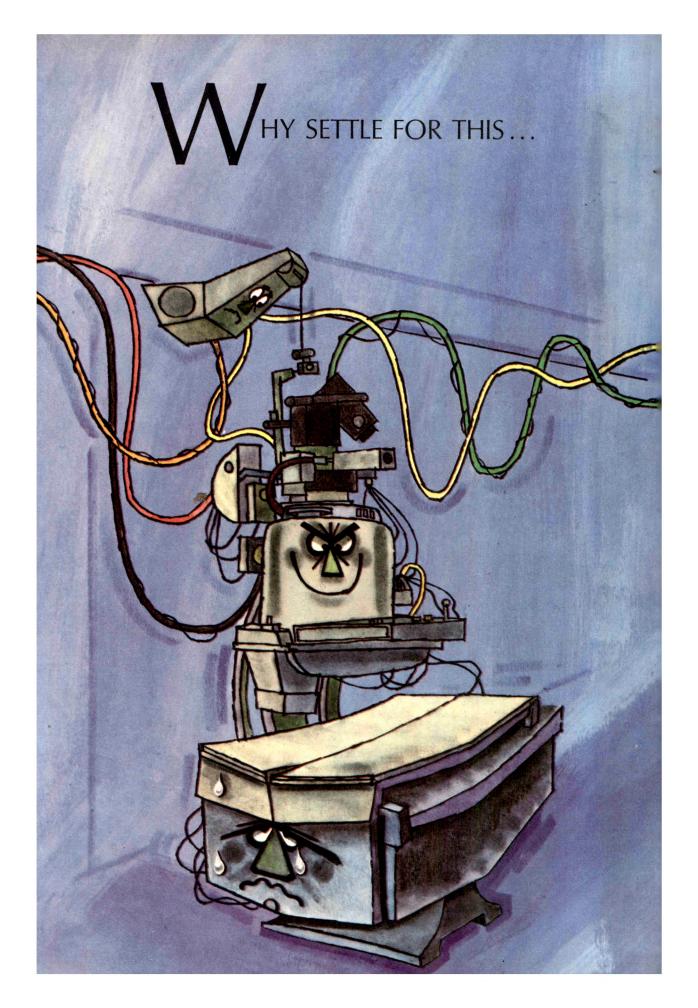
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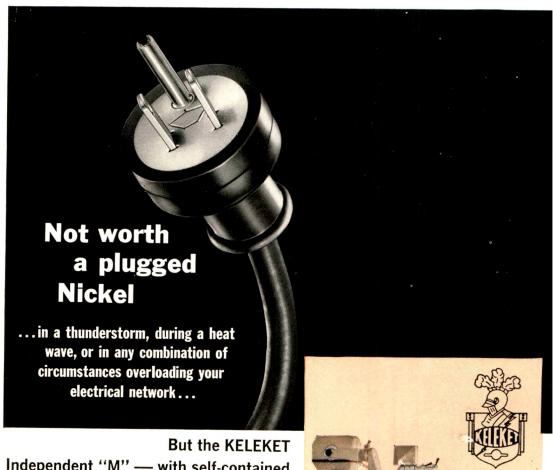
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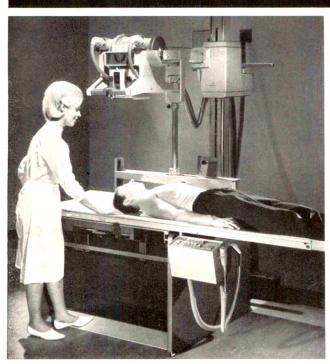


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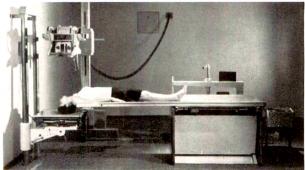
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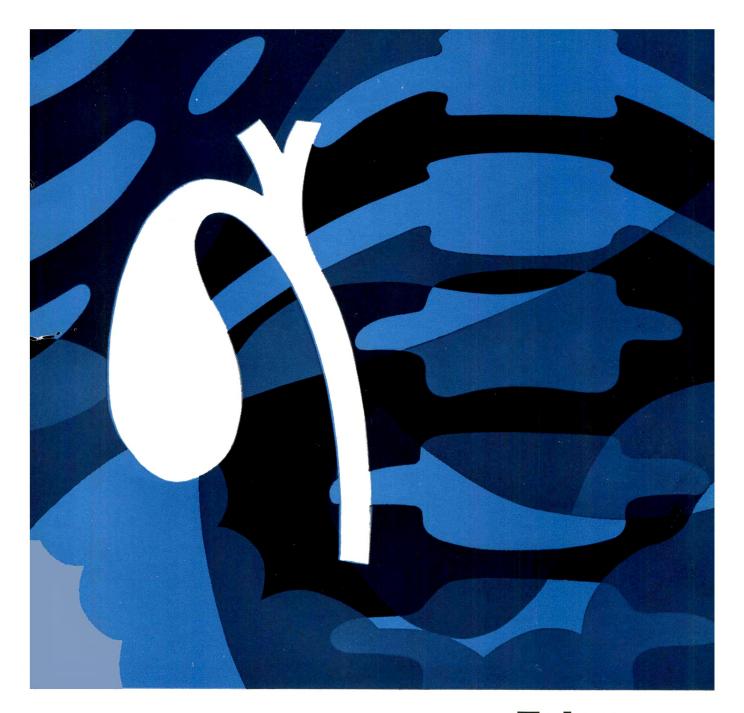


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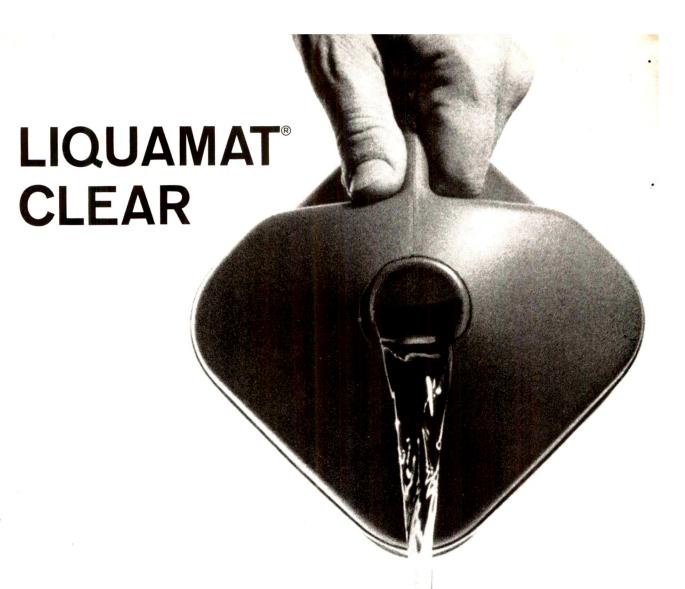
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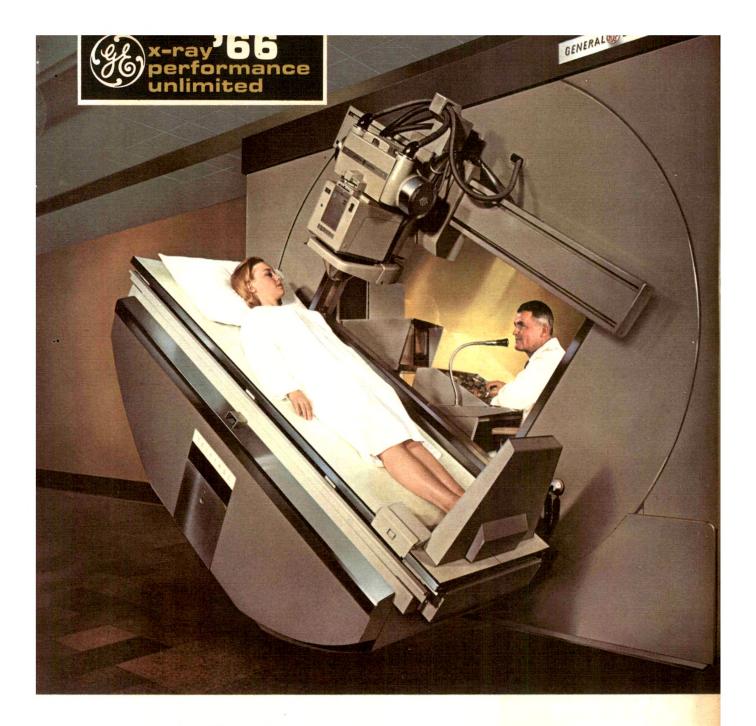
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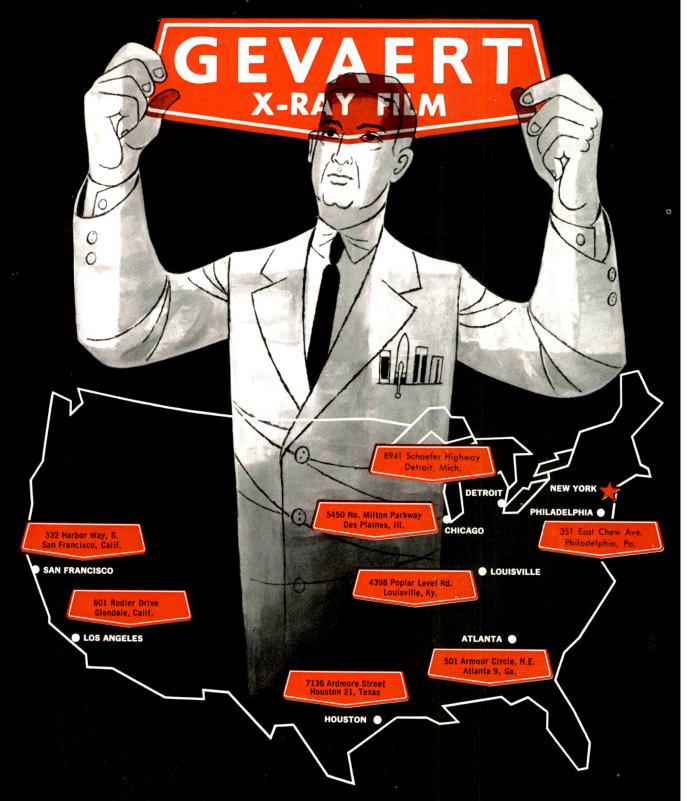
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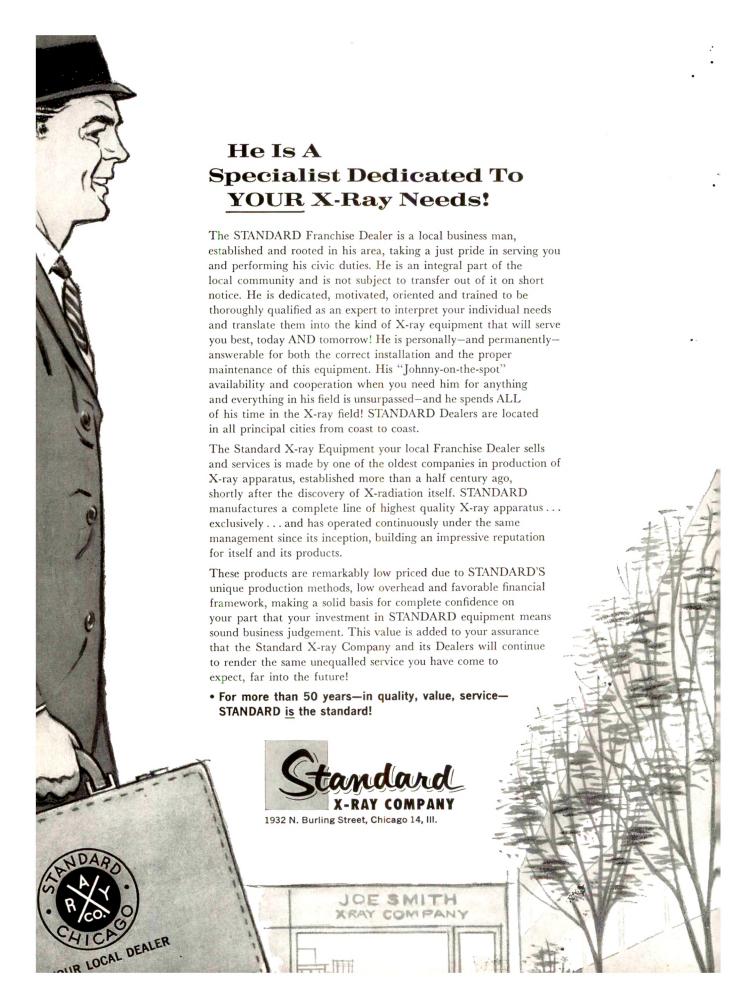
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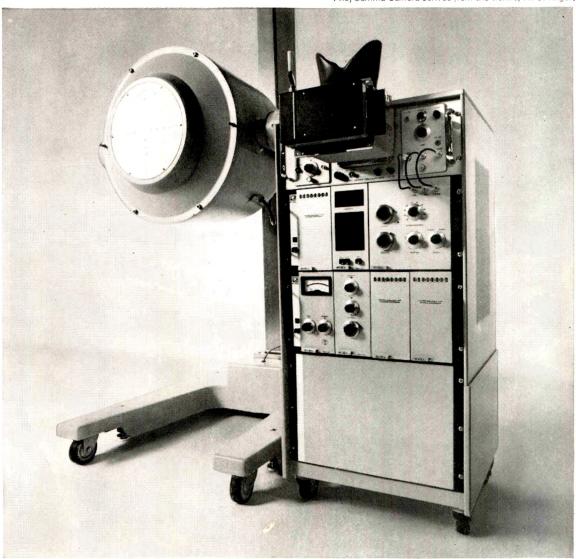


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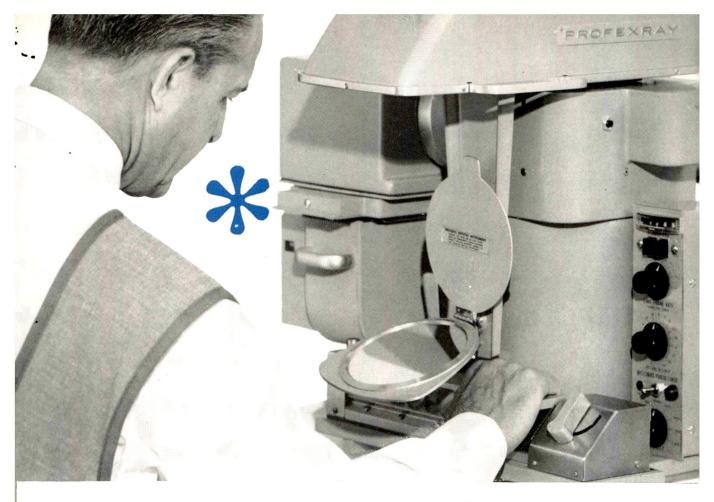


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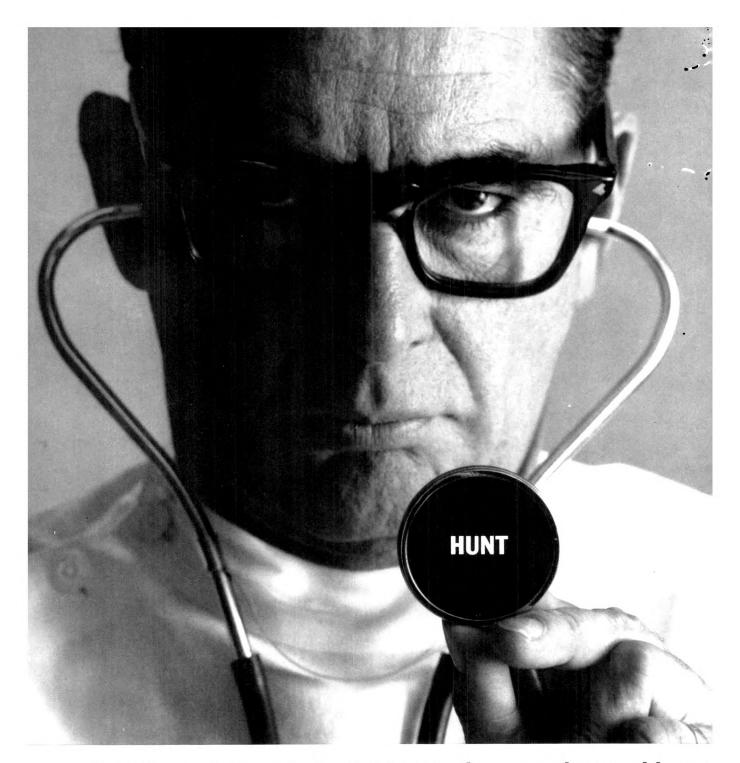
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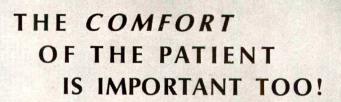
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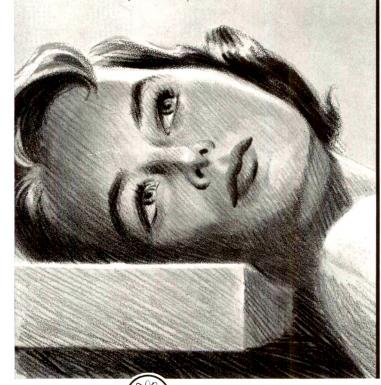
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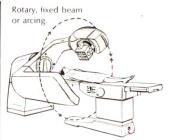
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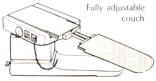
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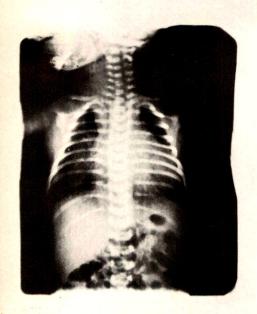
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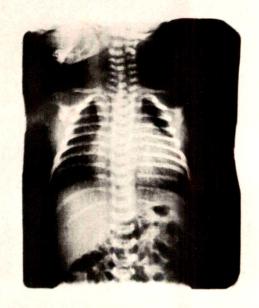
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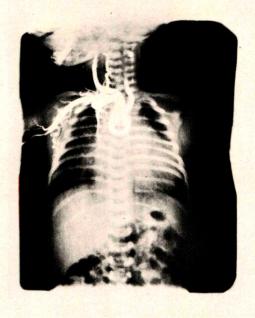
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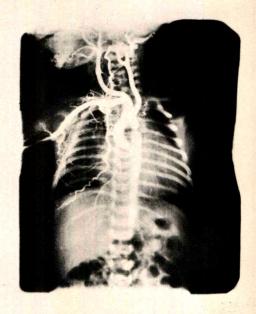




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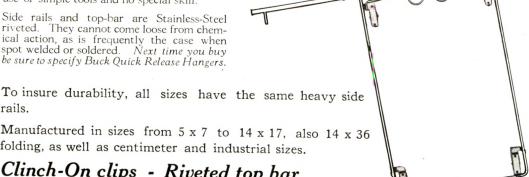
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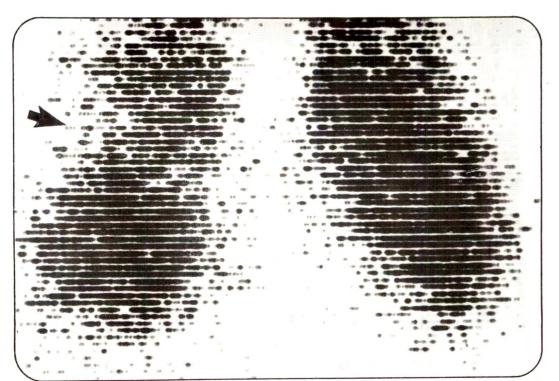
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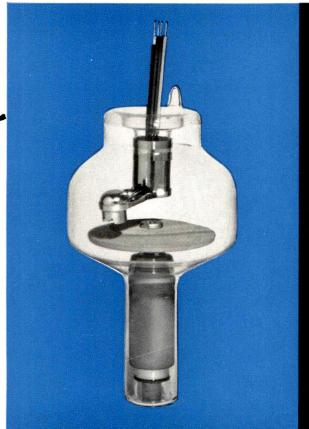
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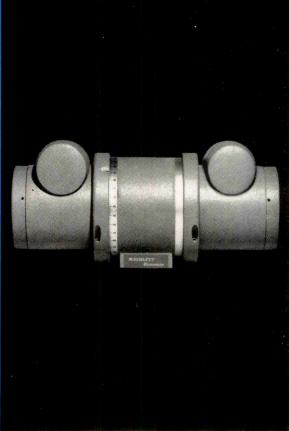
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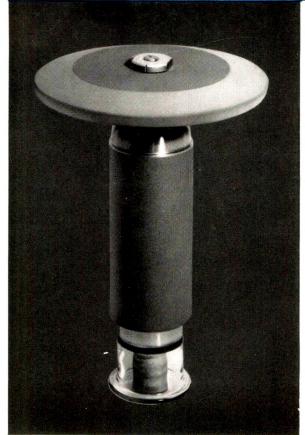
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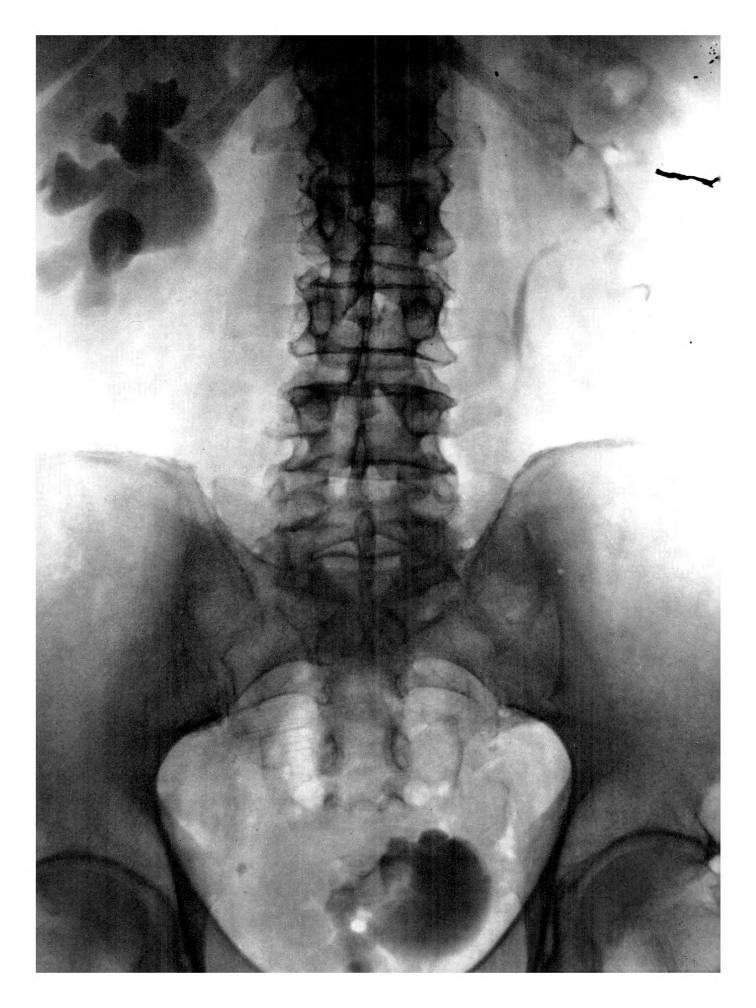


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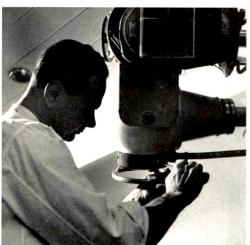
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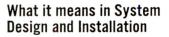
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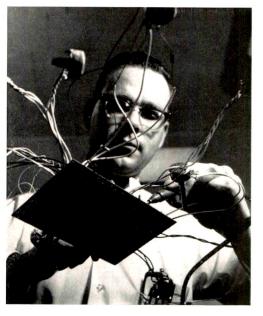
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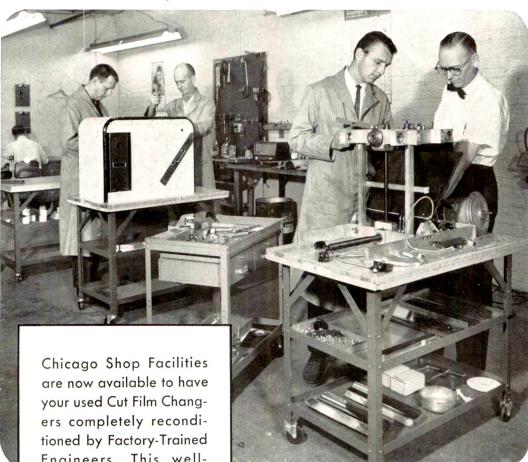
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JOSEPH H. FARROW, M.D.

THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

Vol. 96

JANUARY, 1966

No. 1

PRESIDENT'S ADDRESS AMERICAN RADIUM SOCIETY, 1965*

By JOSEPH H. FARROW, M.D. NEW YORK, NEW YORK

CONSIDER it a high honor to have the dress on the threshold of the fiftieth anniversary of this Society. In reviewing the Addresses of my predecessors, I find that many praiseworthy and timely subjects have been presented. Although approached in a variety of ways, the common denominator has been the application of scientific knowledge to the care of patients, particularly those suffering from neoplastic diseases. Today, for various reasons, medical, economic and political, we are facing new challenges and opportunities that have short-term probabilities and long-term possibilities for improving the quality and quantity of care for all cancer patients.

There are now about 1,000 local clinics or tumor services which have been approved by the American College of Surgeons. These are distributed throughout this country among more than 5,000 accredited hospitals. These clinics to improve and extend care for the cancer patient are the result of many years of active interest, planning and voluntary work on the part of

various clinical specialties in cooperation with and at the initiation of the American College of Surgeons and the American Cancer Society. In some areas, state and municipal health departments have made valuable contributions to this program. The number of patients who have benefited by this approach is not known. It is generally recognized that a great deal has been accomplished in the full utilization of local skills and facilities by cancer-teaching days, by the presentation of problem cases at tumor conferences and by visits of consultants from medical centers, universities or large metropolitan hospitals. This program has avoided the unnecessary transportation of patients to other areas when equivalent treatment has been available locally and, on the other hand, has frequently expedited transfer when special services and equipment were necessary. Furthermore, local interest in diagnosis and treatment has been stimulated and the initial patient-physician relationship main-

The increasing number of radical opera-

^{*} Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8-10, 1965.

tions which can be performed safely, the more frequent use of ionizing irradiation and the various methods for palliating advanced cancers have greatly extended the need for accommodations and expensive facilities. In this age of progressive inflation and taxation, many community and metropolitan hospitals dependent on voluntary contributions can no longer afford all the essentials for limited specialization and up-to-date care for the cancer patient. Support by grants-in-aid would enable local services to use government funds without federal control. This approach would have the immediate advantage of improving and developing community cancer clinics for diagnosis and treatment as well as providing valuable information for planning the correct location and size of new regional centers. It might well avoid a great deal of the superplanning and overmanagement which take so much and provide so little at the bedside.

Cancer hospitals and centers were primarily established to render extraordinary services for the cancer patient by the concentration of highly specialized personnel and equipment. They have also functioned as areas for postgraduate training and clinical investigation; in recent years some have expanded into preclinical research. Cancer institutes have, for the most part, been concerned with basic research and they provide relatively few, if any, accommodations for patients. In this country only 1 of the 17 establishments falling into one of the above categories is now under complete federal control.

It is to be noted that there are, throughout this nation, medical centers, numerous university and large metropolitan hospitals which not only provide equivalent services for patients but also take an active part in clinical investigation and, to a certain extent, basic research. Many of the large nonprofit hospitals are staffed by qualified specialists but most, if not all, are under severe economic strain in providing accommodations and expensive diagnostic and therapeutic equipment. With more generous support from government funds. departments of oncology or cancer-treating teams to include surgeons, radiologists, chemotherapists, internists and pathologists could be organized not only in these but other large hospitals and thereby rapidly improve both the breadth and depth of cancer services which are either lacking or need to be better organized or expanded. Such support would provide more opportunity for combined therapy by the highly specialized services in these areas. It could also serve to establish a more unified liaison with community clinics and, by continuity, avoid piecemeal therapy in the complex and complicated cancer cases. Provision should also be made to include rehabilitation programs. They may mean the difference between mere existence and worthwhile living for some of those subjected to radical cancer therapy.

In recent years the national government, through its various departments and agencies, has shown an increasing interest in the cancer problem. This has been demonstrated in a variety of wavs but mainly by numerous grants-in-aid for postgraduate training, clinical investigation and, particularly, basic research. Many of the complex facilities which created the atomic bomb are now being used to prepare and investigate radioactive materials used not only in microbiological and biochemical research but in the diagnosis and treatment of human cancer. It is, however, somewhat noteworthy that to date most of the progress in treatment and actual care of the patients with cancer has been very little dependent on government funds.

The current recommendations of the President's Commission on Heart Disease, Cancer and Stroke are not just a step but, if approved, a tremendous leap by the national government into the diagnostic and the therapeutic fields. One does not question the sincerity or the praiseworthy efforts of the medical and nonmedical members of the Commission in preparing this report which emphasizes the need and suggests means to reach the ultimate goals

that have long been sought. It is hoped the intent is not to direct and control the treatment of these diseases but to support and assist it by all possible means. Undoubtedly the report, which is being publicized and widely circulated, will arouse great hopes and have a large emotional appeal to the average citizen. Those more directly involved, however, such as congressional representatives, government health agencies and, particularly, the nonfederal medical profession, will face many problems in deciding what to do as well as what not to do.

First, there will be the legislative problem of determining the total amount of tax revenues which will be allocated for this huge and, in some respects, speculative program. Second, there will be the administrative problem of deciding priority and the proportion of the appropriated funds to be used for diagnosis, treatment, education and training, clinical investigation, animal experimentation and basic research. Third, there is the more difficult task of recruiting not only man-power but brainpower for such a gigantic undertaking. One cannot expect spectacular achievements from hastily trained or unwilling participants. At the clinical level there is already a short supply of therapeutic radiologists, particularly of those qualified in the use of megavoltage equipment. Further, there is an expanding need for well-trained clinical investigators and medical scientists to bridge the gap between basic science and clinical application.

In order to provide organized leadership and expedite the development of a program to further the control of cancer by available means, there is an urgent need for a joint committee that is truly representative of all the specialties and organizations most active in the diagnosis and treatment of cancer. The committee should be composed of presidents and presidents-elect or representatives from the executive committees of the specialized societies as well as the chairmen of the cancer committees of the various accrediting colleges. It could, by joint discussion and unified action, provide much needed advice and practical suggestions for the distribution of federal funds at the clinical level. This would avoid therapeutic dogmatism and domination by special interests. It should hasten the distribution of up-to-date care for all patients as well as improve the relationship between the medical profession and the public they wish to serve without political pressures.

In concluding, I would like, first, to have it clearly understood that my comments are spoken as an individual to and not for this Society. Second, I have been selective in my comments although the parts of the report of the President's Commission relating to cancer cover a wide field of medical and scientific interest. My selection does not imply that other aspects of the report are not equally important or worthy of consideration. Finally, in order to preserve the patient's freedom of choice and to face the challenge and opportunity of making the best treatment for cancer nationally available, a great deal will depend upon our individual and collective efforts. Basically, the problem is and will be who will treat what and where.

112 East 74th Street New York, New York 10021



BUCCAL MUCOSA CANCER IN SOUTH INDIA*

ETIOLOGIC AND CLINICAL ASPECTS

By A. D. SINGH, M.B., B.S., D.M.R.T., F.F.R. (LOND.),† and C. F. VON ESSEN, M.D.‡ VELLORE, SOUTH INDIA

HE high frequency of cheek (buccal mucosa) cancer in South India and other areas of South and Southeast Asia has been known since the last century. The close association of this disease with the ubiquitous habit of betel quid chewing has earned it the sobriquet of betel or betel quid cancer. Many observers have noted a particular association between the presence of tobacco in the betel quid and development of cheek cancer. This study is intended to explore this possible relationship, as well as to present the clinicoanatomic manifestations of the disease as seen in Vellore and the staging according to principles of the T.N.M. system. Subsequent reports will deal with histopathologic aspects of these lesions, premalignant manifestations, and the therapeutic approaches and results.

REGIONAL ANATOMY

The site is often defined by a process of exclusion such as buccal cavity, NEC (not elsewhere classified) or NOS (not otherwise stated).*

By general understanding, the buccal mucosa (for want of more precise terms) is the mucosal lining of the cheeks, extending from the line of closure of the lips anteriorly to the retromolar trigone posteriorly and the gingival mucosa medially. Because the gingival mucosa merges with the buccal mucosa in the buccogingival sulcus, a frequent site of lesions, the 2 sites, buccal mucosa and gingiva, are usually grouped together. The buccinator sulcus posteriorly is in close proximity to the pterygomandib-

* See the International List of Diseases and Causes of Death, rubric 144 (Cancer of other and unspecified parts of the mouth).

ular space, involvement of which can result in widespread functional disabilities.11

The vertical sites of contiguous involvement include the mandible and maxilla, and the spaces of the pterygopalatine fossa and the temporal fossa. Lymphatic drainage is toward the upper anterior and posterior superficial cervical chain by way of periosteal and facial lymphatics. Laterally, the parotid gland, the masseter, facial muscles, and the skin may be involved by contiguous spread. With exception of scattered mucous glands and Stensen's duct, the entire mucosa consists of stratified squamous epithelium on a well-vascularized and elastic submucosa.

CLINICAL MATERIAL AND METHODS

During the years 1962 and 1963, 3,529 new cancer cases among a total of 136,000 patients were registered at the Christian Medical College Hospital, located in Vellore, North Arcot District, of Madras State. Of these, 362 (10 per cent) were found to have carcinoma of the buccal mucosa or gingiva. Eighty-three per cent of these cases had biopsy confirming the diagnosis of epidermoid carcinoma. The hospital records were reviewed in addition to interviews of 131 patients by means of a detailed questionnaire including social, dietary, smoking and chewing habits, and clinical details of the oral mucosa, teeth, tumor location and appearance. The pathologic specimens of 34 patients treated by surgery were reviewed.

OBSERVATIONS

DEMOGRAPHIC AND ETTOLOGIC FEATURES

A comparison of frequencies between Connecticut and North Arcot District was

Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8–10, 1965.

This investigation was supported in part by a grant from the American Cancer Society, Connecticut Division, Inc.
† Section of Radiation Therapy, Christian Medical College and Hospital, Vellore, South India.
‡ Section of Radiation Therapy, Yale University School of Medicine, New Haven, Connecticut: Visiting Associate Professor, Christian Medical College Hospital, Vellore, South India.

Table I

COMPARISON OF RELATIVE CANCER FREQUENCIES BETWEEN CONNECTICUT AND NORTH ARCOT DISTRICT

	Connec	ticut ^t	North Arcot ²		
Site	No. of New Cases	Per Cent	No. of New Cases	Per Cent	
Buccal cavity and pharynx	357	4.0	1,526	33.2	
(buccal cavity NOS,* 144)	(48)	(0.5)	(704)	(15.4)	
Digestive system	2,241	24.9	760	16.6	
Respiratory system	938	10.4	156	3.4	
Breast	1,044	11.6	132	2.9	
Female genital organs	951	10.6	753	16.5	
Male genital organs	571	6.3	108	2.4	
Total, all sites	8.984	100.0	4,562	100.0	

1 Data for 1961, Connecticut Tumor Registry, Connecticut State Department of Health, courtesy of Dr. Henry Eisenberg.

² Data for 1962, North Arcot Government Hospitals, courtesy of Dr. T. D. Taravanar, District Medical Officer for North Arcot District, and CMCH.

* NOS= not otherwise stated.

made with data from the Connecticut Tumor Registry and pooled registration figures from the Christian Medical College Hospital (CMCH) and the government hospitals of the district. These combined facilities account for the great majority of district-wide patient registrations.

The data are presented in Table 1 and show, among others, a striking difference in the relative frequency of cancer defined in rubric 144. It has been noted in material both in Connecticut and at CMCH that over 90 per cent of the lesions in this category are, in fact, located in the buccal mucosa, gingiva, and retromolar trigone and this region will be referred to collectively hereafter as the buccal mucosa.

Data comparing the factors of regional origin, sex, and religion between this series and the general CMC hospital experience show that the diagnosis of buccal mucosa cancer was relatively lower in the Christian patients (8 per cent compared to 14 per cent) and that patients from Andhra Pradesh were relatively more numerous (19 per cent compared to 10 per cent). No other significant differences were noted. The modal age range was 50–54 years. The economic status of patients in the series was estimated as 2 per cent well-to-do, 28 per cent middle-class, and 70 per cent poor.

HABITS

The betel quid habit has been described in detail by Balendra, Muir and Kirk, 14 and Orr. 15 The guid consists of 2 or more of the following: betel leaf, lime (calcium oxide), areca nut, spices, and cured tobacco. The frequency of ingestion varies from an occasional postprandial quid to many throughout the day with retention in the mouth at night. The quid may be chewed and swallowed, or it may be chewed and then retained in a buccogingival sulcus with expectoration of saliva, particularly when tobacco is included in the quid. Figure 1, A and B demonstrates a typical location of the retained quid. Table II shows the pertinent data relevant to chewing and smoking habits. The high frequency of tobacco usage contrasts markedly with general population habits. Sufficient data have not yet been obtained on the laterality of habitual placement of the guid but a distinct impression is that the side commonly used was the left, possibly because the right hand in India is considered "clean" and it is used to directly touch food and the mouth. It is more convenient for the quid to be placed in the left buccogingival sulcus by the right hand.

The frequency and durations of quid chewing are marked in this series. A rationale for the prolonged chewing expressed





Fig. 1. (A) A masticated quid of betel leaf, lime, and tobacco in a frequent resting place, the left buccogingival sulcus opposite the second molar tooth. The quid may remain here for hours or even overnight. After removal, the underlying mucosa in this patient demonstrates inflammatory and reactive changes consisting of hyperemia, telangiectasia, and early leukoplakia. (B) The site is identical to that in A showing more advanced changes and early carcinoma.

by many women was the supposed contraceptive action of the quid. The majority of patients had stopped the habit, mostly within the year prior to presentation. This is undoubtedly because of the development of oral symptoms.

The chewing of tobacco in leaf form or powdered (snuff or khaini) without the betel components was noted in 26 per cent of the patients. Half of these used lime; the rest added no other ingredients.

Only 15 patients denied any contact with tobacco (Table III). These patients, however, were habitual betel quid chewers. The majority of patients had pronounced dental disease, generally marked by calculus, pyorrhea, and jagged teeth.

SPECIFIC SITES

The side of involvement could be determined in 350 cases. As shown in Figure 2 the predilection for the left side was highly significant. The particular site of origin on the lateral buccal surface was determined in 233 cases. Far advanced lesions, naturally, were not suitable for this localization. Figure 3 shows the frequency of apparent origin on a grid system.

It is seen that the mid-inferior buccal mucosa (including the inferior buccogingival sulcus) had a striking frequency of involvement (42 per cent). The postero-inferior mucosa and the angle of the mouth were next in frequency. The site of greatest frequency from these data is, therefore, the left mid-inferior buccal mucosa (p <0.001). No differences in this trend were found when an analysis by sex and religion was performed.

STAGE CLASSIFICATION

The T.N.M. classification according to that proposed by the U.I.C.C. Committee on Clinical Stage Classification and Applied Statistics for buccal mucosa⁹ is shown in Figure 4. The classification for the gingiva is essentially identical. Stage grouping of these T.N.M. categories is also shown. Figure 5 is a comparison of frequencies by

LATERALIZATION OF TUMORS BOTH = 2



p<0.001

Fig. 2. Diagram showing unequal lateral origin of buccal mucosa tumors.

	TABLE II				
FREQUENCY AND	RELATIONSHIPS OF H	HABITS	AMONG	131	CASES

		Betel Quid	Snuff	Smoking
	No.	123	34	45
	Per Cent	95%	26%	34%
	1-5	54%	69%	62%
Frequency	6-10	$^{24}\%$	15%	26%
(per diem)	11-20	15%	8%	9%
	>20	7%	9%	3%
	1-5	6%	18%	8%
Total period	6-10	10%	7%	10%
of use	11-20	17%	$^{25}\%$	30%
(years)	21-30	26%	$^{25}\%$	18%
(years)	31-40	$^{24}\%_{o}$	$_{19}\%$	1607
	>40	17%	6%	18%
Other features		added tobacco	added lime	Bidi—78%
		83%	50%	Cheroot—19%
		added lime		Cigarettes—1 case
		100%		

T.N.M. category and by stage between male and female patients. In both sexes the percentage of cases in Stages III and IV are similar. This finding differs from the usual experience in Connecticut where both the frequency of disease and advancement of disease are significantly lower in women.⁸

The skin was involved with tumor in 132 patients (27 per cent of the series) of which 16 had involvement manifested by dimpling or "tethering," 53 had complete fixation by tumor, and 67 had ulceration. It has been noted in many instances that ulceration may have been promoted by heat cauterization of skin overlying the tumor applied by village "healers." Tris-

TABLE III

Correlations of Habits	No.	Per Cent
No habits	0	0
Betel quid but no tobacco	15	8.7
Tobacco in 1 or more forms	116	91.3
Betel quid and smoking	37	28
Betel quid and snuff	25	19
All three	12	9
No betel quid but smoking	8	$\hat{6}$

mus was a common finding in these cases but was not measured sufficiently to yield data of value. Examples of these tumors are seen in Figures 6, 7, 8 and 9.

Roentgenographic studies were performed on 216 patients and 62 were re-

TUMOR ORIGIN BY SECTOR

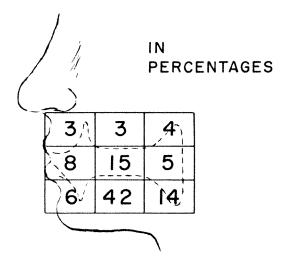


Fig. 3. Diagram showing different rates of apparent origin of buccal mucosa tumors in various portions of the lateral buccal mucosa.

T. PRIMARY TUMOUR

- T1. TUMOUR MEASURING 2 CM. OR LESS IN ITS LARGEST DIMENSION, STRICTLY SUPERFICIAL OR EXOPHYTIC.
- T2. TUMOUR MEASURING 2 CM OR LESS IN ITS LARGEST DIMENSION, WITH MINIMAL INFILTRATION IN DEPTH.
- T3. TUMOUR MEASURING MORE THAN 2 CM IN ITS LARGEST DIMENSION OR TUMOUR WITH DEEP INFIL-TRATION, IRRESPECTIVE OF ITS SIZE.
- T4. TUMOUR INVOLVING OTHER ANATOMICAL STRUCTURES SUCH AS MUSCLE OR BONE EXTENDING TO MORE THAN ONE NEIGHBORING REGION.

N. REGIONAL LYMPH NODES

- NO. NO PALPABLE LYMPH NODES.
- NI. MOVABLE HOMOLATERAL LYMPH NODES
- N2. MOVABLE CONTRALATERAL OR BILATERAL LYMPH NODES
- N3. FIXED HOMOLATERAL OR BILATERAL LYMPH NODES.

M. DISTANT METASTASES

- MO. NO EVIDENCE OF DISTANT METASTASES
- M. DISTANT METASTASES

STAGE GROUPS I 2 3 4 O I II N 2 M IV

Fig. 4. Clinical stage classification of buccal mucosa carcinoma (W.H.O. No. 144).

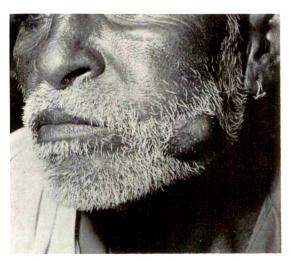


Fig. 6. A common manifestation of buccal mucosa cancer in this series: left lower cheek nodularity with contiguous ulcerated intraoral lesion and destruction of the underlying mandible. The history given was of 40 years of frequent betel and tobacco quid chewing with usual retention of the quid in the left cheek. The lesion was a well-differentiated epidermoid carcinoma. The classification was T4, No, Mo.

	MALES n = 103							= M A		5	
			7	Γ					7	Γ	
		Π	2	3	4			-	2	3	4
	0	0	7	13	24	N	0	- 1	12	17	12
B.I	1	1	-	1	5		- 1	0	1	- 1	4
Ν	2	0	3	13	11	14	2	0	-1	18	14
	3	0	0	4	20		3	0	- 1	12	23
	M	0	0	0	0		M	0	0	0	0

STAGE	NO.	%	STAGE	NO.	%
I	7	6.8	I	13	11.1
П	16	15.5	п	19	16.3
Ш	49	47.5	ш	48	41.0
\square	31	30.2	I	37	31.6

Fig. 5. T.N.M. classification and staging in this series.

ported positive for bone involvement of the mandible or maxilla. Additional details of these cases are shown in Table IV and Figure 10, A, B and C.

TREATMENT

Nearly 60 per cent of the patients were not treated (Table v). The reasons included far-advanced disease, poor general condition, recurrence from previous treatment, and failure of the patients to return. The



Fig. 7. An ulcerated carcinoma with fistula formation. This ulceration was induced by branding of the overlying skin by village "healers." There were marked trismus, mandibular destruction, and fluctuant submental lymph nodes. The classification was T4, N3, Mo.

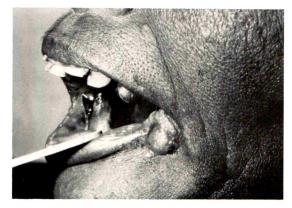


Fig. 8. Carcinoma arising in the buccal mucosa extending past the commissure and involving skin. This patient used "khaini," a mixture of tobacco and lime, and placed it in the anterior inferior buccogingival sulcus in a manner similar to snuff-dipping in the United States. Note the heavy deposits of calculus on adjacent teeth. The classification was T₃, No, Mo.

remaining received either conservative or radical radiation therapy (30 per cent) or surgery (9 per cent).

GROSS PATHOLOGY

The specimens of a selected sample of patients who had surgical resection were studied for clues concerning the pattern of spread, tumor vascularity, and nature of bone destruction.

One-half of the cases had bone involvement of which close to one-half demonstrated erosion or excavation of the mandible rather than tumor infiltration. This finding was also noted in the roentgenographic studies. The distinction between expansile and poorly invasive carcinomas and infiltrating carcinomas appeared to divide the operated lesions into 2 approximately equal groups. Lymph node invasion occurred often by direct continuity and late in respect to the extent of the primary growth. The lower neck was rarely involved. Distant metastases (below the clavicle) were not seen in this series at the time of initial examination. The histopathologic features will be presented in a later paper.

Table IV

ROENTGENOGRAPHIC FEATURES IN 52 CASES

OF BONE INVOLVEMENT

	No.	Per Cent
Side		
right	21	40
left	31	60
Side		
mandible	48	92
maxilla	4	8
Length <1	3	6
of 1-2	7	14
involve- 2-3	17	34
ment 3-4	9	18
(cm.) 4-5	9	18
> 5	7	I 4
Type of bone erosion		
smooth	15	30
irregular	14	28
"moth eaten"	24	48
Pathologic fractures	5	10

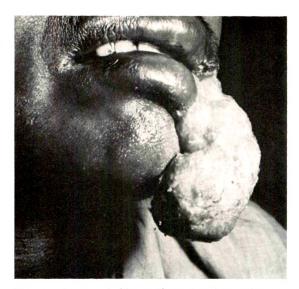


Fig. 9. A remarkably exuberant epidermoid carcinoma arising in the left buccal mucosa and involving the entire left cheek, gingiva, and floor of mouth. There was marked trismus. The lesion appears to erupt through the commissure and is entirely dependent from the oral mucosa. The classification was T4, N1, Mo.

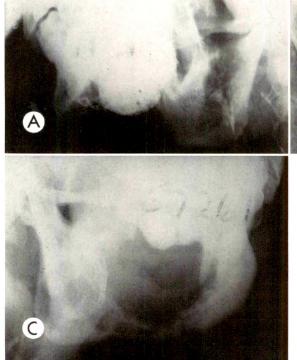




Fig. 10. (A) Roentgenogram of patient with barium impregnated betel quid located in the buccogingival sulcus. Compare the location with that in B and C, roentgenograms of patients with progressively greater bone destruction by tumor. The early cases appear to have more sharply defined excavations compared to the more "moth-eaten" involvement of the cases with pathologic fracture.

Table V
TREATMENT

	Type of Treatment	No.	Per Cen
Radiation	Orthovoltage roentgen therapy	22	6
	Co ⁶⁰ teletherapy	66	18
	Interstitial implantation	22	6
		-	
	Subtotal	110	30
Surgery	Local excision	4	I
	Hemimandibulectomy	16	4
	Hemimandibulectomy and suprahyoid neck dissection	5	I
	Hemimandibulectomy and radical neck dissection	8	2
	Subtotal	33	9
		33	
Radiation and	d surgery	8	2
No treatment		211	58
Total		362	100

DISCUSSION

Betel cancer of the buccal mucosa among Indians is associated with the history of prolonged usage of tobacco in the betel quid or in the form of snuff (Khaini).^{3,6,13–17,19} There remains, however, a small percentage of patients in this series (8.7 per cent) and in the reports by Shanta and Krishnamurthi (5.2 per cent)²⁰ who denied the use of tobacco in the quid or in any form.

Study of matched controls by Shanta and Krishnamurthi demonstrated that the betel quid habit without tobacco is practiced by about 50 per cent of the population, but that only 10 per cent utilize tobacco incorporated in the quid. In a comprehensive study of the total adult populations of 4 villages, Singh²¹ found that 56 per cent of the population chewed betel quid, 28 per cent chewed tobacco in one or more forms, and 25 per cent chewed betel quid without tobacco.

Prolonged contact of the quid with the mucosal site is suggested as an important etiologic factor by the following facts: high incidence at specific sites and left-sided dominance, matching the observed wide-spread habit of placing the quid in these locations, and high frequency and long duration of the habit among affected individuals.

Atkinson et al.2 found that betel cancer was not associated with tobacco incorporation in the quid in New Guinea. In view of the small percentage of Indian patients denying tobacco habits, the possibility that factors other than the tobacco leaf also participate in the genesis of the neoplasm must be considered. These factors include other ingredients, particularly lime (a most irritating substance), vitamin and other nutritional deficiencies and the time factor of duration of contact to the mucosa, relatively independent of the composition of the quid. It seems probable, however, that tobacco remains as the most potent carcinogen in this process. Experimental support for the carcinogenic activity of unburned tobacco has been demonstrated by Bock, Moore and Crouch,⁵ while Muir and Kirk¹⁴ produced carcinoma from extracts of the ingredients of the betel-tobacco quid.

The clinical manifestations of these lesions show many similarities to tobacco chewers' and snuff-dippers' cancers reported in the United States by Friedell and Rosenthal,⁷ Ackerman,¹ Rosenfeld and Callaway,¹⁸ Stecker *et al.*²² and many others.

These relatively localized, slow-growing lesions invade by expansion as often as by infiltration. Bone destruction is common and trismus develops as a result of involvement of the masseter and other masticating muscles. By staging, the lesions seen in India appear more advanced probably by reason of fear and ignorance of the affected individuals. Although curability by resection or irradiation has been favorably reported in the United States, to the situation is reversed in this series because of the advanced nature of these tumors.

Prevention by public education and improved living standards is possible and should be pursued. For the large number of cases presently appearing with advanced disease, new therapeutic concepts must be explored in order to increase the survival rate. Clinical trials of promising chemotherapeutic agents, alone and in conjunction with radiation therapy and surgery, may offer significant improvement.¹²

SUMMARY AND CONCLUSION

Tobacco is probably the principal, but not sole carcinogen in the development of betel quid cancer of the buccal mucosa. The evidence for direct contact as an important co-factor is suggested by the findings of a high incidence at specific mucosal sites generally used for lodgement of the quid. The left side is significantly more frequently involved than the right side. The tumors occur in females as often as in males.

The patients generally present with advanced lesions. Skin ulceration, trismus, mandibular destruction and even patho-

logic fractures of the mandible are frequent findings. The lesions can be classified by the T.N.M. system. Although the degree of local invasion is high, lymph node metastases appear late and remain regional. These cases appear suitable for clinical trials with chemotherapeutic agents, irradiation, and surgery.

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ROENTGENOGRAPHIC PATHOLOGIC CORRELATION OF CARCINOMA OF THE GINGIVA INVOLVING THE MANDIBLE*

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THE roentgenographic appearance of carcinoma of the gingiva involving the mandible is so characteristic as to permit pathologic staging. Only occasional reference has been made in the literature to this problem. According to statistics reported by the American Cancer Society,² Bhaskar,¹ and Tiecke and Bernier,⁵ approximately 8,400 patients each year are seen with carcinoma extending into the mandible. At the M. D. Anderson Hospital, a review of 460 unselected patients having squamous carcinoma of the oral cavity disclosed that 97 of the tumors (21 per cent) had invaded or eroded the mandible (Table 1).

Pathologic study of the 100 squamous cell carcinomas of the gingivae revealed that 56 had extended into the mandible. Roentgenographic examination correctly demonstrated mandibular lesions in 49 of the 100, 29 were correctly reported to exhibit no tumor extension to the mandible, 13 were false positive, 5 were false negative, and 4 were equivocal diagnoses (Table II).

ROENTGENOGRAPHIC FEATURES

In more than 100 roentgenographic examinations of the mandible, definite differences between erosion and invasion were observed.

EROSION

The term "erosion" should be applied to the typical roentgenographic signs of extension into the bone, *i.e.*, perforation of the periosteum, loss of cortical continuity (usually along the superior margin of the alveolus), a U-shaped excavation of the medullary bone, or a punched-out or scal-

Table I
SQUAMOUS CARCINOMA OF THE ORAL CAVITY WITH
EXTENSION 1NTO THE MANDIBLE

Primary Site of Carcinoma	No. of Cases	Patients with Extension to Mandible
Buccal Mucosa	80	15 (18.7%)
Floor of Mouth	80	8 (10.0%)
Tonsil	60	8 (13.3%)
Tongue	80	4 (05.0%)
Gingivae	100	56 (56.0%)
Retromolar Trigone	60	6 (10.0%)
Total	460	97 (21.0%)

loped lesion (Fig. 1, 2 and 3). These changes are caused by pressure of the gingival tumor, rather than by infiltrating tumor cells. The lesion is radiolucent. No reaction in the periosteum or the adjacent bone is apparent. There is no evidence of bone produc-

TABLE II

ROENTGENOGRAPHIC AND PATHOLOGIC DIAGNOSES

OF MANDIBULAR EXTENSION OF 100

GINGIVAL CARCINOMAS

Re	entgenogra Diagnosi	Diag	ologic nosis	
	Negative	Equivocal	Positive	
62			49	13**
	34		5	29
	01	4*	2	1
Total			56	43

^{*} One patient whose roentgenographic diagnosis was equivocal was lost to follow-up.

^{**} Erosive carcinoma.

^{*} From the University of Texas M. D. Anderson Hospital and Tumor Institute.

[†] Section of Diagnostic Radiology, Department of Radiology.

¹ Department of Surgery.

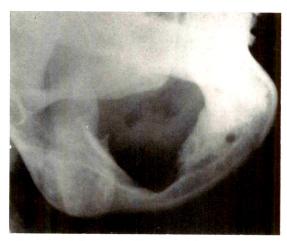


Fig. 1. Mandibular erosion from Grade II carcinoma of the gingiva. Note sharply outlined typical Ushaped excavation without apparent changes in adjacent bone.

tion within the excavation. The base of the "U" is generally well delineated, much as an egg placed neatly in the holder of an eggcrate. The tumor producing the erosive lesion is histopathologically Grade I or II. Grade I and II gingival carcinomas produce the erosive type of mandibular lesion that is generally commensurate with the intraoral growth (Fig. 4, A and B). Some of the false

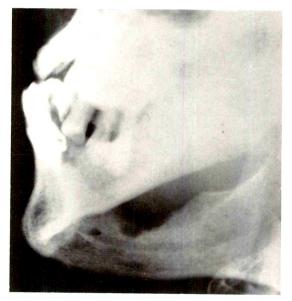


Fig. 2. Grade II carcinoma producing the "erosive" defect in the mandible. Histopathologic examination showed no tumor in the osseous structure.

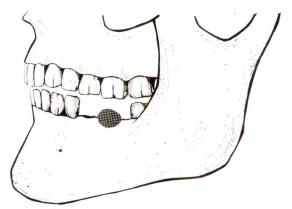


Fig. 3. Diagram showing the characteristics of an "erosive" lesion, Grade 1 and 11: (1) intraoral size equals the measured size of the mandibular defect; (2) margins of mandibular defect are smooth; and (3) the defect is lucent.

positive diagnoses of mandibular invasion were based upon observations of erosive lesions. Microscopic examination revealed no invasion of the bone.

INVASION

The term "invasion" should be applied only to actual infiltration of the malignant squamous cells into the medullary bone. This infiltration is most often observed in Grade III lesions, and exhibits on the roent-genogram small, diffuse patches of osseous degeneration in which spicules of bone are apparent. Also, the margins of the superior alveolar cortex are poorly defined (Fig. 5 and 6). The more rapidly growing Grade III tumors produce an invasive mandibular defect which is generally much smaller than the intraoral lesion of the soft tissues (Fig. 7, \mathcal{A} and \mathcal{B}).

DISCUSSION

Histologic examination of specimens most often shows osteomyelitis; however, in the untreated cases, roentgenographic criteria of osteomyelitis are lacking. The margins of the erosive lesions studied were generally sharp, without reactive change or sequestration. This appearance suggests that periosteal perforation by erosive lesions is delayed; the tumor fills in the defect which it creates, and thus prevents the

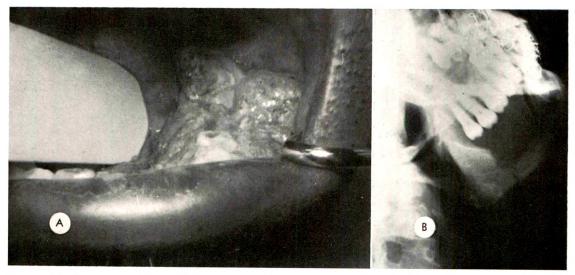


Fig. 4. (A) Grade II carcinoma of the gingiva. Note size of lesion. (B) Mandibular extension from gingival carcinoma, Grade II, shown in A. The mandibular and intraoral lesions are commensurate. A pathologic fracture is present.

infiltration of bacteria into the bone. Osteomyelitis accompanies mandibular invasion: however, the tumor is usually predominant and signs of osteomyelitis are not apparent. In the majority of the Grade III and IV tumors of this series, the bone was invaded so rapidly that the periosteum did not have time to exhibit a reaction.

The roentgenographic differentiation of invasive carcinoma, osteomyelitis, and os-

Fig. 5. Mandibular invasion by gingival carcinoma, Grade III. Industrial film was used in this examination. The mandibular defect is infiltrative.

teoradionecrosis of the mandible may be difficult. The latter two conditions are characterized by sclerosis or condensation, sequestration, periosteal reaction, and the formation of new bone. Although spicules of bone are observed with invasive carcinoma of the mandible within the zone of the destruction, the spicules of bone are of the same roentgenographic density as the adjacent normal bone.

Roentgenograms of the mandible are always indicated before definitive therapy

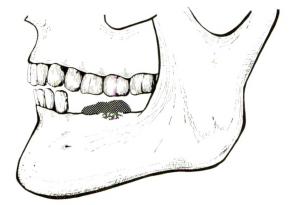


Fig. 6. Diagram showing the characteristics of an "invasive" lesion Grade III: (1) intraoral size is larger than the mandibular defect; (2) margins are irregular; and (3) spicules of bone are seen within the zone of destruction.

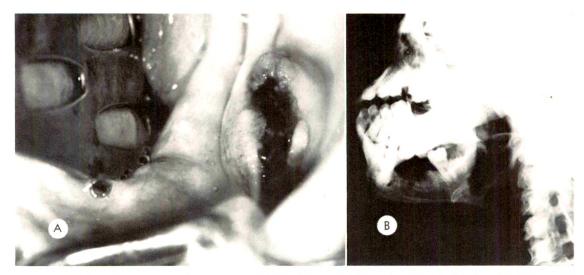


Fig. 7. (A) A large fungating carcinoma of the gingiva, Grade III. Note size of intraoral lesion. (B) Note small lesion in the mandible as compared to the size of the intraoral tumor shown in A.

is instituted. Involvement of the mandible, when present, must be accurately diagnosed prior to therapy. Post-therapy roent-genograms of the mandible in carcinoma of the oral cavity are also extremely valuable as a base line in the evaluation of recrudescent tumor versus a surgical defect, or the defect of osteoradionecrosis.

SUMMARY

In a review of 460 cases of intraoral carcinoma, 21 per cent of the lesions were found to erode or invade the mandible. Of 100 carcinomas of the gingivae, 56 had extended into the mandible.

The roentgenographic criteria of differentiating erosive and invasive defects of the mandible secondary to carcinoma of the gingiva are presented. The pathologic correlation, indicating that the erosive lesions are Grade 1 or 11 and the invasive lesions of higher grade malignancy, has been established.

Erosive lesions may be adequately treated by radiation therapy or surgery. If surgical removal is performed, a local excision rather than hemimandibulectomy is adequate.

Invasive lesions are not amenable to radiation therapy. Hemimandibulectomy is indicated for these lesions.

Recognition of the roentgenographic pathologic correlation of erosive and invasive lesions of the mandible secondary to carcinoma of the gingiva will markedly improve the cosmetic and therapeutic results in patient care.

Erosive carcinoma of the mandible, that is, the mandibular defect without histopathologic evidence of invasion, accounted for 13 false positive roentgenographic interpretations. Recognition of the erosive lesion will markedly improve diagnostic accuracy which, in turn, will provide a rational therapeutic approach.

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MYXOMA OF THE MAXILLA*

PREOPERATIVE IRRADIATION TO FACILITATE RESECTION

By JOSEPH N. ATTIE, M.D., ANDREW CATANIA, M.D., D.D.S., and SEYMOUR BRENNER, M.D.

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M YXOMAS are rare tumors. Although there are myxomatous areas in many benign and malignant tumors of mesenchymal origin, true myxomas as distinct neoplasms are occasionally encountered. Stout⁷ reported 143 cases of myxoma of which 10 were in bone; of the latter, 5 were in the jaws. Zimmerman and Dahlin¹¹ reviewed 2,276 bone tumors seen at the Mayo Clinic; they found 26 instances of myxoma in the jaws but no cases in other bones. Lichtenstein⁶ stated that he had never encountered a bone tumor that warranted the diagnosis of myxoma. Gorlin et al.4 reviewed the literature in 1961 and found a total of 31 acceptable cases to which they added 3 of their own.

It is the purpose of the authors to report 2 patients with very large myxomas located in the maxilla and encroaching upon the floor of the orbit. In both instances preoperative irradiation resulted in shrinkage of the tumors, permitting complete resection of the lesions without sacrificing the orbital floor.

REPORT OF CASES

Case I. R.L., a 43 year old white female, was admitted to the Maimonides Hospital on December 16, 1962 with a history of having had a tooth pulled in the right upper premolar region 6 weeks prior to admission. At that time the dental roentgenogram disclosed a density in the right antrum and there was slight swelling of the alveolar region around the tooth. A biopsy was performed and revealed myxoma of bone. Roentgenographic evaluation of the right antrum by tomography (Fig. 1A) showed a large spherical tumor which was opaque and filled practically the entire right antrum, extending upwards to the orbital plate in the roof of the antrum. There was some erosion of

the bone forming the orbital plate. Because of the encroachment of the tumor on the orbit, preoperative radiotherapy was instituted prior to admission to the hospital. Cobalt 60 teletherapy was delivered to the right antrum through a single anterior field, shielding the eye; 200 rads were administered daily to a total dose of 4,000 rads in 28 calendar days. Roentgenograms at the completion of radiotherapy (Fig. 1B) showed regression of the tumor with separation of its upper margin from the orbital plate. On the day following admission, resection of the right maxilla was performed through an oral approach without sacrificing the floor of the orbit and a skin graft was inserted into the defect. The tumor was well encapsulated and removed intact (Fig. 2A). The skin-lined maxillary defect (Fig. 2B) was subsequently fitted with a prosthesis attached to the remaining teeth. An excellent cosmetic and functional result was obtained (Fig. 5A) and there has been no recurrence to date.

CASE II. F.M., a 43 year old Negro female, was admitted to the Long Island Jewish Hospital on May 17, 1964 with a history of having had a tooth extracted from the left upper molar region about 2 years prior to admission. Following the extraction, a swelling persisted in the area and a biopsy at that time revealed a myxoma of bone. The tumor was locally excised and curetted with temporary improvement, but the lesion soon recurred and progressed in size, causing swelling and distortion of the maxilla. About 3 months prior to admission, roentgenographic evaluation of the left antrum by tomography (Fig. 3A) showed nearly complete opacification of the left maxillary antrum with thinning out and decreased density of the left orbital plate, apparently the result of pressure by the very large soft tissue mass within the maxillary sinus. Again, in the hope of sparing the floor of the orbit, a course of preoperative radiotherapy was administered. Co-

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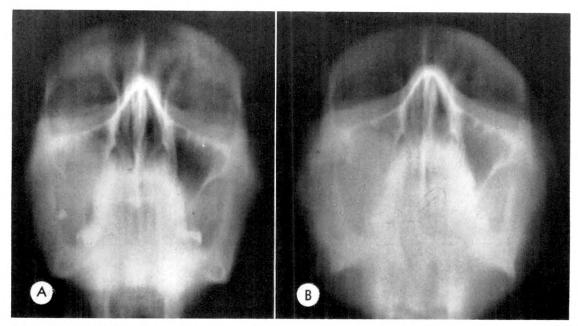


Fig. 1. Case 1. (A) Tomogram shows large spherical tumor filling most of the right maxillary antrum and causing erosion of the bone of the orbital plate. (B) Tomogram following 4,000 rads of cobalt 60 radiation shows regression of the tumor. The upper margin of the lesion is better defined and separated from the orbital plate which has apparently become recalcified.

balt 60 teletherapy was delivered to the left antrum through a single anterior field, shielding the eye; 200 rads were given daily to a total dose of 4,000 rads in 28 calendar days. Tomograms taken at the completion of radiotherapy (Fig. $_3B$) showed regression of the tumor; its margins became more clearly defined and there was increased opacity of the orbital plate. It seemed that the pressure of the tumor

on the bony roof of the antrum had caused pressure necrosis and the shrinkage apparently resulting from radiotherapy was sufficient to permit the bone to recalcify. Prior to admission to the hospital, impressions were taken of the jaws in this patient as well as in Case I in order to prepare a prosthesis without delay. The patient was operated upon on the day following admission and the left maxilla was resected

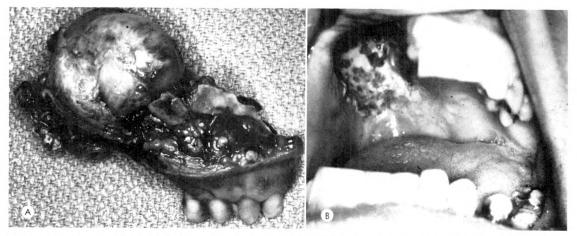


Fig. 2. Case i. (A) Resected hemimaxilla with large encapsulated myxoma of right antrum. (B) Healed maxillary defect lined with split thickness skin graft.

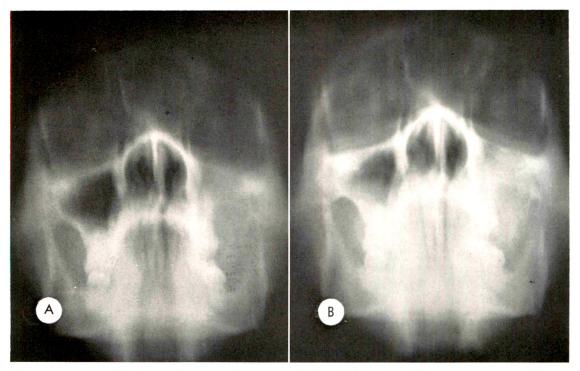


Fig. 3. Case II. (A) Tomogram shows nearly complete filling of the left maxillary antrum by a soft tissue tumor extending up to the orbital plate which is partially eroded and thinned out. (B) Tomogram following 4,000 rads of cobalt 60 radiation shows shrinkage of the tumor away from the orbital plate which is more sharply outlined and opacified.

through a combined intra-oral and Weber-Ferguson skin incision without sacrificing the orbital floor. After removal of the bulky, well encapsulated tumor with the maxilla (Fig. 4A), the defect was covered with a split thickness skin graft (Fig. 4B). When the healing was complete, a prosthesis was inserted and at-

tached to the remaining teeth. The postoperative course was uneventful. An excellent cosmetic and functional result was obtained (Fig. 5B).

Comment. In both cases the prior preparation of impressions permitted early

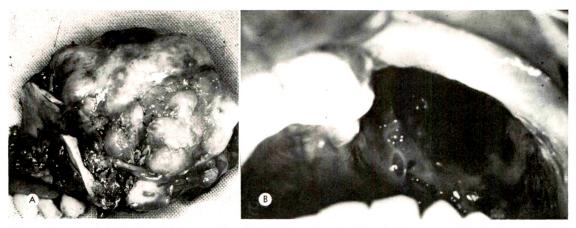


Fig. 4. Case II. (A) Resected hemimaxilla with bulky myxoma filling left antrum. (B) Healed maxillary defect lined with split thickness skin graft.

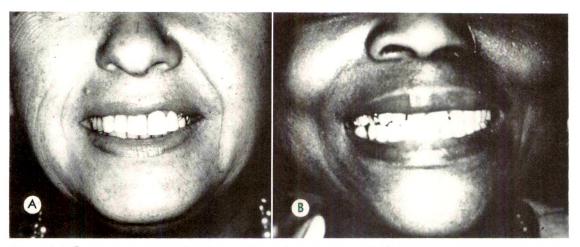


Fig. 5. (A) Case I. Appearance of patient with prosthesis in place. (B) Case II. Appearance of patient with prosthesis in place. Note the excellent cosmetic result.

rehabilitation of the patient. The surgery was performed under general anesthesia administered via a preliminary tracheostomy. The external carotid artery on the side of the resected maxilla was ligated in continuity immediately prior to the procedure producing a completely dry field.

DISCUSSION

ORIGIN

Myxomas and myxofibromas of the jawbones are benign tumors, apparently of odontogenic origin. They probably arise from the mesenchymal portion of the tooth germ rather than from mesenchymal cells which are destined to produce bone. This hypothesis is supported by the fact that in nearly all cases studied the tumors were associated with unerupted or missing teeth.⁸ Furthermore, the cellular elements of myxomas resemble the stellate cells of the dental papilla and the dental follicle of the tooth germ.

In contrast to myxomas that occur in the mandible and maxilla, myxomas of the long bones arise from cells that are osteogenic. When myxomas occur outside of the facial bones, they are usually more malignant. Although some authors, such as Willis, 10 believe that myxomas of soft tissues are merely variants of fibromas containing mucin in the intercellular spaces, Stout⁷ con-

siders them true neoplasms. They are usually slow growing and locally invasive, and except for those arising in the heart, they do not metastasize.

The rarity of myxomas is attested to by their complete absence in large series of bone neoplasms reported by Geschickter and Copeland³ and Jaffe.⁵

INCIDENCE

Myxomas occur with equal frequency in males and females. The mandible and maxilla are equally affected. About two-thirds of the cases occur between the ages of 10 and 30. In the mandible, the most common sites are the angle, the horizontal ramus and the region of the molar teeth. In the maxilla, the most frequent locations are the molar region, as in the 2 patients presented, the zygomatic region, and, least often, in the anterior maxillary region.

ROENTGENOLOGIC FINDINGS

Early lesions generally appear as well-defined radiolucent areas with sclerotic margins, more often multilocular than unilocular. A fine trabeculation or honeycombed structure is often seen. In the alveolar region, the margin becomes scalloped between the teeth. With increasing size, the tumor invades the antrum, at first only showing clouding, later producing a

large rounded mass of soft tissue filling a large portion of the antrum. The walls of the antrum are at first expanded and later destroyed by the tumor. It is often difficult or impossible to differentiate the myxomas from cysts, fibrous dysplasia or ameloblastomas by roentgen studies.

PATHOLOGY

Myxomas present a bosselated surface, are soft or firm depending on the proportion of the fibrous element, and grayish-white to yellowish or amber in color. A capsule may or may not be present. The cut surface is translucent and glistening. There is a varying degree of expansion of the surrounding bone with perforation of the cortex in the larger tumors. Infiltration of adjacent tissues is sometimes observed, especially in myxomas that recur following limited resections. The clinical behavior of these tumors bears a resemblance to that of ameloblastomas.

Histologically, the tumor is essentially composed of stellate cells possessing long cytoplasmic processes that anastomose with each other. A variable number of normal-appearing fibroblasts are also found. There is a basophilic cytoplasm with an ovoid, hyperchromatic nucleus. The intercellular substance is mucin; rarely, collagen is present. One may find strands of epithelial cells, especially along the edge of the tumor, representing foci of odontogenic origin. Mitoses are rare.

TREATMENT

A combination of enucleation and curettage has been the most common method of treatment employed. Because of the location of these tumors in the mandible and maxilla plus the benign designation, more radical *en bloc* resections have only been performed on very large myxomas. Consequently, as in the case of ameloblastomas and salivary gland mixed tumors, local recurrences have been frequent. In the series of 26 myxomas reported by Zimmerman and Dahlin,¹¹ 25 per cent were recurrent when first seen by the authors and of those cases treated by them about 25 per cent subsequently recurred.

Radical resection of the mandible or maxilla for more extensive myxomas has been reported by Wawro and Reed. They and other authors 1 state that radiotherapy is probably of no value in the management of myxomas of the jawbones. In several of their cases, however, Zimmerman and Dahlin supplemented surgical therapy with postoperative irradiation. This was done either because of an erroneous malignant diagnosis or because they felt that the removal of the tumor was incomplete.

PREOPERATIVE IRRADIATION

The concept of radical surgery following intensive high energy irradiation has been tested in numerous malignant neoplasms in the region of the head and neck; more recently, the technique has been extended to the treatment of cancer of the lung, esophagus, uterus, etc. The rationale of the preoperative use of irradiation was discussed by Fletcher and Jesse.2 They asserted that the peripheral extensions of the tumors were more radiosensitive than the central areas because of the better oxygenation of the periphery, where the blood supply was best. The irradiation, usually ranging from 4,000 to 5,000 rads, often reduced the volume of the tumor, permitting the operative procedure to be smaller in scope and more thorough. Furthermore, by reducing the viability of the tumor cells, the possibility of implantation in the wound is diminished. Buschke and Galante¹ favor preoperative irradiation of tumors that have invaded locally and specifically recommend it in cases of bone involvement. By judicious administration of radiation, limitation of dosage, and careful planning of the interval between irradiation and surgery, one may avoid damage to vascular structures and connective tissues and thereby prevent interference with wound healing and reduce postoperative morbidity.

The purpose of radiation therapy in a

benign tumor, such as myxoma, is not different from its preoperative use in malignant tumors. The principle is to shrink the tumor sufficiently so that the surgical margins may be more adequately defined and thus spare the vital structures surrounding the tumor while permitting total extirpation. The 2 patients presented with large myxomas involving the antrum and extending to its bony walls so that the upper limits of the tumor could not be separated roentgenographically from the floor of the orbit. In view of the curability of these lesions when completely excised and in order to ensure optimal cosmetic results, it was decided to irradiate the lesions preoperatively and perform the surgical procedures 4 weeks later. The patients were treated with a Picker C-1,000 cobalt 60 teletherapy unit using a fixed beam technique. The treatments were given at a 50 cm. target skin distance through a 4×4 cm. field. The field encompassed the entire antrum including the orbital plate. The eve was protected by a lead block. A dose of 200 rads was delivered daily for a total of 4,000 rads. In both patients, the upper borders of the tumors receded sufficiently to be roentgenographically distinguishable from the bony floor of the orbit, thus ensuring the integrity of the orbit and its contents following maxillary resection.

PROGNOSIS

Myxomas of the jaws are slow growing tumors, patients presenting with histories ranging from a few weeks to 12 years. Although the tumors are benign and have not been reported as a cause of death, they recur rapidly if incompletely resected and may invade extensive portions of the upper and lower jaws and extend into the surrounding soft tissues. They sometimes reach an enormous size and produce marked deformity. The tumors may destroy the bony walls of the maxilla and break into the nasal cavity or orbit.

SUMMARY

Two patients with very large myxomas located in the maxilla were observed in whom the tumors encroached upon the floor of the orbit. In both cases, preoperative irradiation resulted in sufficient shrinkage of the tumors to permit complete resection of the lesions without sacrificing the orbital floor.

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SILASTIC MOLDS OF A NASOPHARYNGEAL TUMOR DURING RADIATION THERAPY*

By GALEN B. COOK, M.D., and RAUL MERCADO, Jr., M.D. COLUMBIA, MISSOURI

SEQUENTIAL observations of disease during treatment may be useful to the practitioner, instructive to the student and encouraging to the patient. For these reasons we have studied the nasopharynx of a woman undergoing radiation therapy for undifferentiated epidermoid carcinoma using a new diagnostic test recently described.¹

A permanent, three-dimensional, surface impression of the nasopharvnx can be obtained by introducing 20 ml. Silastic 382† blended with 10 ml. Medical Fluid 360† and the vulcanizing agent stannous octoate. Prior to casting, the subject is anesthetized topically with a pontocaine spray and placed in Proetz position. The resulting mold is stable after 4 minutes and may be easily extracted transorally for inspection and cell recovery. Surface detail is exact thus the reverse-image cast serves well as a means to locate the tumor accurately and to become a lasting record of the cancer's surface size and configuration and its radiation response. Including the time required to induce anesthesia, the entire process requires no more than 15 minutes.

REPORT OF A CASE

M. I. B. (EFSCH: 65-33961) is a white insurance secretary, 44 years of age, who noted incomplete nasal airway obstruction and consulted her family physician. He prescribed symptomatic medications but after 8 weeks the complaints persisted and a mass was palpable high in the left cervical chain. Treatment was continued for an additional 8 weeks when the patient was referred to a rhinologist. This physician detected a nasopharyngeal tumor and referred the patient to the Ellis Fischel State Cancer Hospital for further evaluation and treatment

Indirect mirror nasopharyngoscopy showed a

2×3 cm. embosselated mass in the midline of the posterior wall of the nasopharynx. A single 4 cm. hard tumor was palpated just posterior to the angle of the mandible in the left cervical lymph node chain. A silastic mold was made of the nasopharynx (Fig. 1A) showing an eroded defect (negative image) on the posterior nasopharyngeal wall extending superiorly to within 7 mm. of the nasal septum and laterally to the salpingopharyngeal folds. The margins of the tumor were over-riding, suggesting a polypoid configuration. The exact size of the tumor was 26×21×8 mm. A volume of 1.46 cc. presented above the surrounding surface of the nasopharynx. Cytologic examination of cells recovered from the surface of the mold did not show cancer cells, but a biopsy of the mass was interpreted as undifferentiated epidermoid car-

The lateral laminagrams of the nasopharyngeal area showed a 2×3 cm. soft tissue mass in the posterior nasopharynx encroaching upon the nasopharyngeal air pattern. Radiation therapy was given by means of a cobalt 60 teletherapy apparatus. The primary tumor and the metastatic neck lymph nodes were treated with large parallel opposed fields. A tumor dose of 4,000 r was delivered to the primary tumor, while the metastatic lymph nodes received a tumor dose of 4,500 r. Additional radiation was then given to the tumor in the nasopharynx using anterior oblique fields. A total tumor dose of 6,200 r was delivered to the primary tumor. An additional 2,000 r were delivered to the neck lymph nodes by means of tangential fields. The entire course of treatment lasted 46

Midway during the course of treatment (eighteenth day), a second nasopharyngeal impression was made (Fig. 1B). This mold showed reduction in the volume of the nasopharynx attributable to edema from treatment. The tumor was significantly smaller, measuring IIXIIX4 mm. The superior margin of the mass had regressed from the nasal septum and the over-all contour had changed to a sessile configuration.

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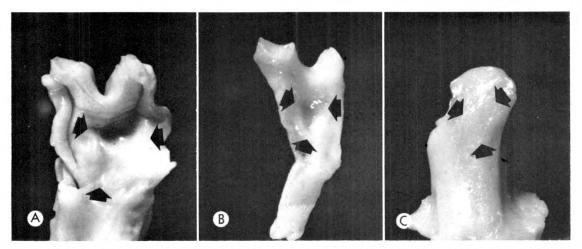


Fig. 1. Photographs of silastic molds showing the posterior wall of the nasopharynx. Arrows mark periphery of tumor, (A) Beginning of treatment. (B) Midway in treatment. (C) Completion of treatment.

The volume of the tumor above the surface of the surrounding tissues was 0.13 cc.

On the day preceding the final radiation treatment, a third nasopharyngeal mold was made (Fig. 1 C). No tumor was detectable. The area where the cancer had been present was now smooth and level with the surrounding mucous membrane. An examination of the neck showed no lymphadenopathy.

During 8 months of follow-up examinations, the patient has continued to be free of signs

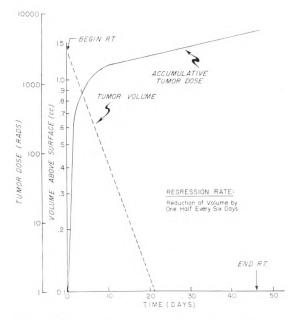


Fig. 2. Relation of tumor regression to radiation dosage.

and symptoms of persistent or recidivous cancer.

DISCUSSION

A plot was made of the cancer's volume above the surface of the nasopharynx during the course of treatment (Fig. 2). These data were obtained by filling the defect on the mold with paraffin, weighing the paraffin mass, and converting to cubic centimeters by multiplying the weight and the specific gravity of paraffin (0.89). If the technique is repeated in other cases, a day-to-day graph of tumor regression may be plotted as a means of learning more of the time-dose relations of various cancers during irradiation.

By referring to the nasopharyngeal mold, the resident radiotherapist gained a precise visual guide as to the size, configuration and location of this cancer. Thus, he was better able to relate the pathologic tissue to the surrounding normal anatomy and appreciate the radiotherapeutic plan.

Considerable psychologic benefit was derived by the patient when she was able to understand the location and nature of this disease and see its response to treatment.

We think this simple, inexpensive and accurate technique has value in the radiation treatment of tumors of the nasopharynx; we encourage others concerned with this problem to explore its usefulness.

SUMMARY

The pattern of response of an undifferentiated epidermoid carcinoma of the nasopharynx has been followed during radiation treatment by making silastic molds of the area. Information gained through this adjunct is illustrated and discussed.

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ANALYSIS OF COMPLICATIONS FOLLOWING MEGAVOLTAGE THERAPY FOR SQUAMOUS CELL CARCINOMAS OF THE TONSILLAR AREA*

By BURTON P. GRANT, M.D., † and GILBERT H. FLETCHER, M.D. ‡ HOUSTON, TEXAS

TUMORS of the tonsillar area include tumors arising in the tonsillar fossa, retromolar trigone and anterior tonsillar pillar which yield a high percentage of control by radiation therapy. In order to deliver cancerocidal doses of radiation to the areas involved by tumor, high doses are given to the underlying mandible, and radionecrosis of the mandible has been one of the more serious complications arising from irradiation of these lesions.

From 1954 through 1962, 176 tumors of this area have been treated with curative intent by 1 of 6 techniques employing megavoltage radiation. Cobalt 60 external beam therapy using 5 different field arrangements has been the mainstay of treatment. In a few patients, a portion of the therapy has been given with a 22 mev. betatron unit.

The external beam techniques used have been as follows:

- 1. A single homolateral field.
- 2. Parallel opposing fields with equal doses given to each field.
- 3. Parallel opposing fields with more radiation given on the side of involvement.
 - 4. Paired wedge filtered fields.
- 5. A single homolateral field supplemented with kilovoltage radiation delivered through an intra-oral cone.
- 6. A small group of patients was treated with external beam therapy, supplemented by interstitial implantation of radioactive gold grains or radium needles.

These various techniques have not been used concomitantly but have evolved through the years. The single field homolateral technique with cobalt 60 teletherapy was used in earlier years for T_1 and T_2 lesions of the anterior faucial pillar-retromolar trigone and abandoned because of marked subcutaneous fibrosis. With this arrangement high doses were delivered through the mandible to the area of disease. The dose at the level of the mandible was of necessity higher than that attained at the deeper areas of tumor involvement. An apparent advantage of such a technique is the sparing of tissues on the contralateral side of the oropharvnx.

Since 1961, the wedge pair technique has been used for most T₁, T₂, and some T₃ lesions of the anterior faucial pillar-retromolar trigone and selected ones of the tonsillar fossa. Paired wedge filter fields tend to limit the radiation to the side of involvement without producing a marked gradient in the radiation level as one proceeds from the surface inward toward the lesion. The technique requires accurate dosimetry and because it is a localized type of treatment, carries with it the hazard of geographic miss.

Equally loaded parallel opposing fields deliver a relatively homogeneous amount of irradiation from surface through the tonsillar area. The parallel opposing field technique with 1:1 or 1:2 loading has been used for lesions extending close to the midline, anaplastic tumors of the tonsillar fossa, and/or when whole neck irradiation is indicated.

Unequally loaded parallel opposing fields

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deliver more radiation to the area of involvement with slight sparing of the contralateral side.

The single homolateral field supplemented by intra-oral cone is more easily adaptable to early lesions but carries the added risk of geographic miss. The various types of external irradiation supplemented by interstitial implantation of radioactive sources allow less extensive irradiation to large volumes with the external beam and yet deliver cancerocidal doses to the more resistant components of the disease.

Since one may select any of several of these techniques, it seems worthwhile to analyze the results from the standpoint of complications produced, with particular reference to osteonecrosis. Other complications such as dryness of the mucous membranes, laryngeal edema, facial edema, trismus, hearing loss, and rupture of the carotid artery were also studied.

BONE EXPOSURE AND RADIONECROSIS OF THE MANDIBLE

Radionecrosis of the mandible is a complication which may arise following heavy irradiation of the mandible. The effect of the irradiation on small blood vessels about the mandible appears to be the primary underlying factor. When the overlying mucous membrane is interrupted either by trauma, local necrosis of the membrane, or by dental surgery, infection may enter the mandible and precipitate osteitis. Pain is usually severe when bone is exposed. Some mandibulectomies were performed for relief of pain and not because of osteitis.

Poor oral hygiene is a contributing factor, offering a site of entry for infectious organisms. The reduction of salivary gland function secondary to direct action of irradiation on the salivary glands produces a dry mouth. This results from the absolute reduction in the amount of saliva produced and also from a qualitative change which results in the production of a more viscous secretion. The resulting saliva removes food particles surrounding the teeth less effectively and contributes to the

development of poor oral hygiene.⁴ This feature has been so prevalent that therapists have advised prophylactic removal of the molar teeth prior to heavy irradiation of the mandible.

Bone exposure with or without radionecrosis of the mandible occurred in 66 of the 176 patients studied, an incidence of 37.5 per cent. (Patients with primary necroses of the soft tissue structures about the tonsillar area were included in this group because the mandible was exposed.) Three patients developed areas of necrosis at two separate times during the followup observation, so that a total of 69 bone exposures were studied.

Fifty-seven of the 69 bone exposures developed within the first year of the follow-up period, 41 of these within the first 6 months; 7 developed during the second year, and 4 during the third year following treatment; a single instance was observed 71 months following treatment for the primary lesion. Fourteen of the 19 patients who required mandibulectomy for necrosis developed their necrosis during the first 9 months of the follow-up period. Figure 1 shows the time of onset of the complications.

Many of the bone exposures were of a mild and temporary nature. Twelve of the 69 persisted 1 month or less, and a total of 50 persisted less than 1 year. Forty-three of the 69 (62.3 per cent) healed on conservative therapy. Nineteen (27.5 per cent) were of such severity as to require

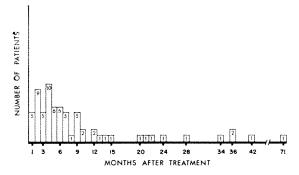


Fig. 1. Time of onset of bone exposure following treatment.

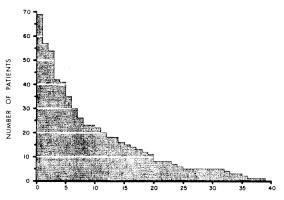


Fig. 2. Duration of bone exposure in months.

hemimandibulectomy. The remaining bone exposures (10.2 per cent) were in patients who died before healing had taken place. Figure 2 shows the number and the duration of each bone exposure.

CLINICAL FACTORS IN MANDIBULAR COMPLICATIONS

AGE OF PATIENTS

Most of the patients treated for lesions of the tonsillar area fell into the 50 to 69 year age group (103 of 176 patients treated). Thirty patients were less than 50 and 43 patients older than 69. Table 1

Table I

Bone exposures according to age groups

Age (yr.)		No. of Necroses	Per Cent
Less than 50	30	16	53+4
50-59	50	20	40.0
60-69	53	21	39.6
70-79	36	8	22.2
80-	7	1	14.3

SEVERE NECROSES REQUIRING MANDIBULAR SURGERY

Age (yr.)	No. of Patients	Necroses	Per Cent
Less than 50	30	7	23.3
50-59	50	5	10.0
60-69	53	3	5.7
70-79	36	4	11.0
80-	7	0	

lists the number of patients developing bone exposure in each age group and those who required hemimandibulectomy. Age does not seem to be a factor in this group of patients; however, if any conclusion is drawn from these data, it would be that patients in the older age groups had a lower incidence of bone exposure than did those in the younger age groups. The results may reflect a tendency on the part of therapists to treat lesions occurring in younger patients more aggressively.

STAGE OF DISEASE

The lesions were staged according to the TNM system. A greater volume of normal tissue is damaged in treatment of advanced lesions through the large treatment fields used for irradiation. Healing following a breakdown of the mucous membrane is inadequate, predisposing to subsequent infection of bone. In Table 11 the patients are arranged by stage of disease with the number of bone exposures occurring in each stage. Although the T₃ and T₄ groups contain a slightly larger percentage of complications, the effect of advanced disease becomes more manifest when one notes that the incidence of severe necroses requiring hemimandibulectomy is much more frequent in the T_3 and T₄ lesions.

Table II

BONE EXPOSURE ACCORDING TO STAGE
OF PRIMARY LESION

Stage*	No. of Patients	No. of Patients with Bone Exposures	No. of Severe Necroses Requiring Mandibulectomy
T_1+T_2 T_3+T_4	88	26 (29.5%) 40 (45.4%)	6 (6.8%) 13 (14.8%)

^{*} T1: Less than 3 cm. in diameter.

T2: 3 to 5 cm. in diameter with minimal extension to adjacent structures.

T₃: Greater than 5 cm. with limited extension to adjacent structures.

T4: Massive.

		TABLE III	I	
DISTRIBUTION	OF TREATMENT	TECHNIQUES	ACCORDING TO	STAGE OF DISEASE

(1991) - 1995 - Marie Park Park Park Park Park Park Park Park	Per Cent Sin		Parallel C		Paired	External	Single Field
Stage	of Entire Group	Single Field	Unequally Loaded	Equally Loaded	Wedge Filters	plus Interstitial	Intra-oral Cone
$egin{array}{c} T_1 \ T_2 \ T_3 \ T_4 \ \end{array}$	17 (9.7%) 71 (40.3%) 61 (34.6%) 27 (15.4%)	3 (6%) 26 (52%) 13 (26%) 8 (16%)	5 (7.8%) 19 (29.6%) 31 (48.5%) 9 (14.1%)	1 (7.2%) 4 (28.6%) 3 (21.4%) 6 (42.8%)	5 (22.7%) 9 (40.9%) 6 (27.3%) 2 (9.1%)	4 (33·3%) 6 (50.0%) 2 (16.7%)	3 (21.4%) 9 (64.2%) 2 (14.4%)

INFLUENCE OF RADIATION TECHNIQUE ON INCIDENCE OF BONE EXPOSURE

Before one can assess what part variation in technique played, one must first look at the distribution of the patients treated with each radiation technique and at the stage of the disease (Table III). It is noted that the groups treated with unequally loaded parallel opposing fields, equally loaded parallel opposing fields and external radiation plus interstitial implantation contain a higher percentage of the T_3 and T_4 lesions.

The incidence of bone complications with each treatment technique is shown in Table IV.

It appears that although the groups treated with equally loaded parallel opposing fields, unequally loaded parallel opposing fields, and external therapy with interstitial implantation of radioactive sources were weighed with more advanced lesions, the incidence of bone exposure in these groups was no more and perhaps slightly less than that in the other groups. This may not be a fair appraisal since all bone exposures have been included, and some of these were of short duration. Although the groups treated with parallel opposing fields contain more advanced lesions, the incidence of severe necroses requiring mandibulectomy in these groups is quite low. It should also be noted that these 2 groups contain 78 cases or 44.3 per cent of the total number of cases.

Although many factors contribute to the development of bone exposure, 2 of the most obvious ones are the volume of tissue irradiated (field size) and the total dose received. The dose of interest is that delivered to the mandible rather than to points in or medial to the tumor. In the patients treated by single homolateral field, the total given dose delivered to the

Table JV

Incidence of Bone exposure and osteonecrosis by techniques

Techniques	No. of Patients	No. of Patients with Bone Exposure	No. of Patients with Necroses Requiring Mandibulectomy
Single homolateral field	50	24 (48.0%)	9 (18.0%)
Unequally loaded parallel opposing fields	$\tilde{6}_{4}$	22(34.4%)	4 (6.25%)
Equally loaded parallel opposing fields	14	2(13.2%)	0
Paired wedge filter fields External irradiation plus interstitial	22	10 (45.5%)	3 (13.6%)
implantation of radioactive sources	12	4 (33.3%)	2(16.7%)
Single homolateral field plus intra-oral cone	14	4 (28.6%)	I (7.1%)

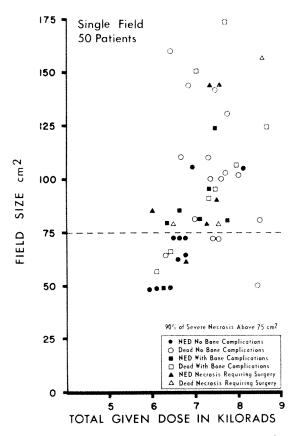


Fig. 3. The "given dose" is the dose measured at the depth of maximum build-up for the particular size field. It is the dose which is used to determine treatment times. Ninety per cent of the severe necroses in patients treated with single homolateral field technique developed in those for whom portals larger than 75 cm.² were used. NED=no evidence of disease.

field was used as the reference dose and plotted against field size. Figure 3 shows, for the patients treated with a single field, that although an obvious distribution pattern is not seen, 20 (38 per cent) of all complications in this group and 8 (89 per cent) of the severe necroses in this group were in patients treated with a field area of 75 cm.2 or more. Sixty-eight per cent of all patients treated by this technique had fields this large. Twenty-one patients received a given dose of less than 7,000 rads. Nine (or 43 per cent) developed complications, 3 requiring mandibulectomy. This is not significantly different from the incidence of complications for the entire group. It would appear that for the dose range employed there was no correlation between dose and necroses.

In the unequally loaded parallel opposing fields, a similar analysis was attempted. Most of these patients were treated with a 2:1 loading so that the given dose to the side of involvement was twice the given dose to the opposite side. For analysis, the given dose to the 2 fields was summed and plotted on a graph with the corrected field size of the most heavily irradiated field. Figure 4 shows the relationship of field size and dose to the occurrence of bone exposure. Although a clear pattern is

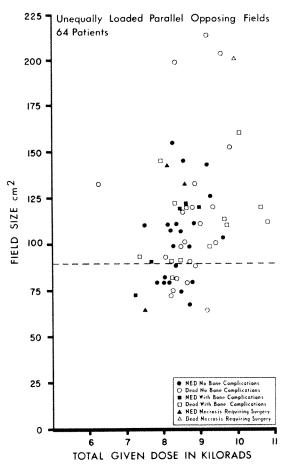


Fig. 4. Nineteen of the 22 bone exposures developed in patients treated with unequally loaded parallel opposing fields with portals larger than 90 cm.². All patients with a summated given dose of more than 10,000 rads have developed bone exposures. NED=no evidence of disease.

not produced, it may be seen that all patients receiving a total given dose in excess of 10,000 rads developed bone complications, whereas only 16 of 60 patients receiving less than this dose developed these complications. Three of 17 patients with fields smaller than 90 cm.² developed complications (17.6 per cent), while 19 of 47 patients (40.4 per cent) with fields 90 cm.² or larger developed complications.

The group of patients treated with equally loaded parallel opposing fields is not large. The given doses to each field were summed and plotted against field size as above. As shown in Figure 5, the 2 patients who received high doses to large fields each developed complications.

With the wedge pair technique, angled wedge filtered fields are employed which

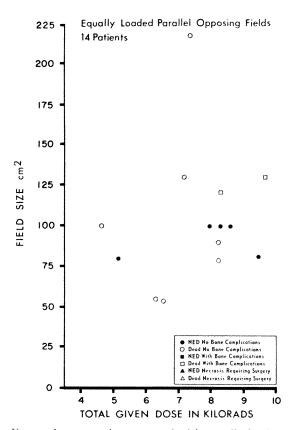


Fig. 5. Among patients treated with equally loaded parallel opposing fields, 2 patients with fields larger than 120 cm.² and summated given doses of respectively 8,250 and 9,500 rads developed bone exposure. NED = no evidence of disease.

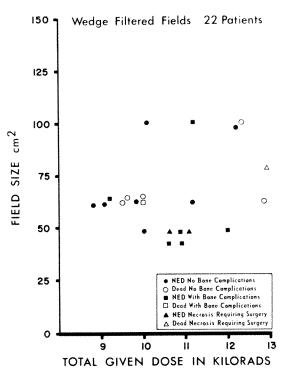


Fig. 6. When the wedge pair technique was used for treatment, bone exposures developed in only 2 patients with a summated dose of less than 10,500 rads and in 8 patients with more than 10,500 rads. Nine bone exposures were self-limiting; 6 were probably precipitated by dental extraction. NED=no evidence of disease.

converge on the tumor from the side of involvement. A dose volume designation similar to that used in the previous technique is employed but cannot be compared with the other groups. The dose is again expressed as a sum of the given doses to each of the wedge fields. With this technique, much of the radiation designated given dose never reaches the patient but is absorbed by the wedge filter. Within this group, however, comparison between individual patients can be made. Figure 6 shows that most of the bone complications are seen in patients who receive more than 10,500 rads (sum of given dose to both fields). This group includes 8 complications seen in 12 patients. Below this dose level only 2 of 10 patients developed complications. Six of the bone exposures were probably precipitated by dental extraction.

The group of patients treated with external irradiation combined with interstitial implantation of radioactive sources (12 patients) developed 4 complications, 2 of which were superficial and self-healing. Two required mandibulectomy. This was a heterogeneous group of patients treated with various techniques of external irradiation so that comparison within the group as to the volume dose effect is not possible. In most instances, the interstitial radiation was given for persistent disease. In the 14 patients treated with a single homolateral field plus intra-oral cone, 4 complications occurred. One required a surgical procedure and the remainder were self-healing. There was no correlation between field size and incidence of necroses. In 3 of the 4 patients developing necrosis, dental extractions were carried out near the beginning of treatment. These bone exposures were all mild and selfhealing.

INFLUENCE OF DENTAL EXTRACTIONS ON SUBSEQUENT DEVELOPMENT OF NECROSIS

Comment has been made concerning the dangers of poor dental hygiene and the part dental trauma may play in the initiation of necrosis of the mandible following irradiation. In this group of 176 patients, there were 20 patients who had dental extractions near the time of the initiation of radiation therapy. Of this group, 3 developed necrosis at or near the site of extraction. Each of these 3 extractions, which subsequently led to the development of necrosis, was done prior to the beginning of treatment. The intervals from extraction to the first day of radiation therapy were 2, 4, and 7 days. The question is raised as to whether this short interval of time did not allow for mucosal healing and, therefore, was a major factor in the subsequent process. In this group of 20 patients, there were 7 additional patients who had dental extractions from I to 7 days prior to the beginning of treatment and 4 patients who had extraction during the course of irradiation. None of these patients developed complications. It appears that although timing of dental extraction may play some part in healing for this group of patients, it was not as important as has been stressed by others. Six patients who had extractions from 6 weeks to 8 days prior to the beginning of treatment had no difficulty.

A much greater problem exists for the patient who must undergo dental extraction after radiation therapy has been completed. Sixteen patients had dental extractions from $1\frac{1}{2}$ to 52 months after the completion of radiation therapy. Seven of these patients developed subsequent mandibular complications. These 7 patients had their extractions at 2, 3, 4, 7, 10, 12, and 30 months after the completion of treatment. In each case precautions were taken to minimize trauma and to prevent infection. Ten of these patients had extractions within I year of completing treatment; of these, 6 developed necrosis. Only 1 of 6 patients who had extractions more than I year after completing treatment subsequently developed bone exposure.

From this experience it would seem that if the eventual need for dental extraction can be anticipated it should be done before the irradiation. The practice of carrying out needed extractions 10 days to 2 weeks prior to the beginning of treatment has merit, but this time factor is probably not as important as it might seem; dental extractions may be carried out during treatment, if necessary, without high risk of subsequent difficulty. One should be particularly careful to avoid dental trauma during the initial year after the completion of radiation therapy.

TREATMENT OF BONE EXPOSURE

The treatment of radiation necrosis of the mandible is first prophylactic. In addition to precautions relative to potential dental problems, care is given to maintain the integrity of overlying soft tissues. This includes the removal of irritating substances, particularly tobacco, hot bev-

•	TABLE	V
OTHER	COMPLI	CATIONS

	Sin	ala.	F		Opposing	*		red	Exte	rnal	~ ,	e Field us		
	Single Field		Unequally Equally Loaded Loaded		ally ided			plus Interstitial		Intra C	i-oral lone	Total		
Dryness of mouth	12/50	24%	22/64	34%	6/14	43%	6/22	27%	3/12	25%	3/14	21%	52/176	30%
Trismus	9/50	18%	3/64	5%	1/14	7%	2/22	9%	2/12	17%	*******	*****	17/176	10%
Hearing loss	2/50	4%	3/64	5%	1/14	7%		normals.		****	1/14	7%	7/176	4%
Facial edema	******		3/64	5%					1/12	8%	*******	sirements	4/176	2%
Laryngeal edema Carotid artery	4/50	8%	8/64	12%	desirable	According to the state of the s		****	(8000-1918)			All All Ph	12/176	7%
rupture	******		4/64	6%	1/14	7%	******	********	1/12	8%	******	*****	6/176	3%

erages, and poorly fitting dentures. If bone becomes exposed, the primary therapeutic approach is conservative with the use of frequent salt and soda irrigations, zinc peroxide packs, and powder spraying. The details of the conservative management have been outlined by Fletcher and MacComb.² Operative intervention is used only when necessary and is most often undertaken because of severe pain. If pain is not a significant factor, prolonged conservative treatment, even over many months, is justified.

OTHER COMPLICATIONS

Other complications encountered in this group of patients were dryness, laryngeal edema, trismus, hearing loss, facial edema, and carotid artery rupture. The true incidence of these complications, particularly that of dryness, is difficult to evaluate. Certainly, it is believed that some degree of dryness is experienced by almost every patient treated for a tonsillar area lesion. When dryness became so objectionable that the patient complained of this aspect during follow-up visits, it was recorded and is manifest in this analysis. Table v shows the incidence of these complications. It is noted that dryness is more common in patients treated with parallel opposing fields and less common where more localized therapy is carried out.

Laryngeal edema was an infrequent complication seen only in patients who had extensive lesions where treatment fields, of necessity, included portions of the larynx. Trismus was seen in each group but was somewhat more common in the patients treated with a single homolateral field. The masseter muscle on the side involved, like the mandible, is heavily irradiated.

Hearing loss refers to mild unilateral loss and was infrequent in its occurrence.

In addition to radiation therapy for the primary lesion, some of these patients had a radical dissection for neck involvement or a combined resection for residual or recurrent disease at the primary site. All patients who developed carotid rupture had surgery in addition to irradiation in the neck area. Although this is a severe complication, most of these patients were salvaged by carotid ligation.

DISCUSSION

Complications arising from radiation therapy and particularly osteonecrosis must be accepted by the radiotherapist. Paterson⁵ states that radionecrosis is a consequence of radical therapy and can be consistently avoided only by systematic underdosage. The incidence of such necroses increases as the therapist treats lesions aggressively for cure, particularly advanced lesions. The acceptable incidence of necroses of 2 to 3 per cent, as cited by Paterson, seems unrealistic. In the excellent monograph by Ennuver and Bataini,1 the ratio of necrosis to successful treatment of lesions of the tonsillar area was 1:4. In their material, osseous necroses were found to develop as late as 16 years following treatment. Since the follow-up period for the present series of patients is limited, the incidence of bone complications in this group (37.5 per cent) may increase with time. This figure of 37.5 per cent is in line with the incidence of necroses in other oral tumors as reported by Mac-Comb.³

SUMMARY

If carcinoma of the tonsillar area is treated aggressively, approximately one-third of the patients will develop some form of complication in the mandible. There will also be significant incidence of less severe complications. Most of the bone exposures, however, will be self-limited or will heal with conservative therapy. There appears to be a decreased incidence of severe mandibular complications when parallel opposing fields are employed.

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PERCUTANEOUS TANTALUM 182 WIRE IMPLANTA-TION USING A GUIDING-NEEDLE TECHNIQUE FOR HEAD AND NECK TUMORS*

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INTERSTITIAL implantation of large tumors for curative purposes is generally ill-advised because of difficulty in obtaining dose homogeneity. The disadvantages of the existing methods are inherent in the physical shortcomings of radium sources. Restriction in the range of sizes and strengths plus frequent gross inaccuracy in the placement of the needles discourage the use of implantation as an initial attack. The existing dosage systems (Paterson and Parker^{4,5} or Quimby²) theoretically call for the best possible geometric precision. Attempts were made by Shapiro and Cohen⁶ to improve the geometric precision by implementing a template.

In our medical center, radiotherapy is employed in many cases of advanced tumors in the head and neck region where cure is remote and palliation by existing means unsatisfactory. Because a large area or volume implant as an initial attack is dismissed, one is left with a limited choice between chemotherapy and/or external beam therapy, infrequently surgical extirpation. We believe our Ta¹⁸² wire technique provides an additional choice for such an undertaking. Implantation of large tumors is possible by this technique because of precise geometry, wider selection of strengths, and flexibility of the wire.

MATERIALS AND METHODS

Ta¹⁸² is a malleable wire, supplied by Atomic Energy of Canada in two sizes, 0.2 and 0.28 mm. in diameter, clad in 0.1 mm. of platinum for beta filtration. Physical factors of Ta¹⁸² are: gamma energy – 1.12

and 1.22 mev.; beta energy - 0.53 mev.; k factor – 6.13 r/hour/mc at 1 cm. The specific activity can vary somewhat depending on the neutron flux in the uranium pile. Tantalum wire has a weight of 0.005 gm./ cm. and, when bombarded in the uranium pile for I week, will give off a specific activity of about 50 µc/cm. for a flux of 1011 neutrons/cm.2/second. Using a pile factor of 4.5, I month's bombardment will impart a specific activity equivalent to 0.66 mc of radium per I cm. of Ta¹⁸² wire.⁷ Its half life is III days. For practical purposes, the decay factor of Ta¹⁸² during the period of implantation can be ignored in dosage calculation.

We have implemented wire-guiding needles from 18 gauge lumbar puncture needles by drilling a hole at the tips (Fig. 1A) to admit the Ta ¹⁸² wire. The needles are held securely by their hubs in a removable aluminum holder (Fig. 1B). This holder is built in such a way that 2, 4 or 6 needles can be held at a 1 cm. distance. A movable space-maintainer (Fig. 1B) is slipped over the needles to prevent convergence or divergence of needles as they are introduced into the tissue.

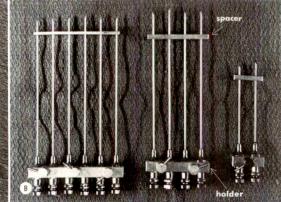
For lesions in the tongue and floor of the mouth, the needles are introduced percutaneously so as to emerge in the oropharyngeal cavity. Combinations of various length needles enable us to encompass the entire tumor mass with ease. Ta¹⁸² is dispensed from a lead jig containing a spool of wire (Fig. 1C). A hairpin is formed around an adjustable graduated plunger-bar by which wire can be severed at the desired length (Fig. 1C). After the ends of the

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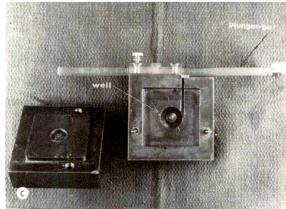


Fig. 1. (A) Photograph showing the guidingneedle with a hole at its tip. (B) Removable aluminum needle-holder and movable spacemaintainer. (C) Lead jig with a central well for a wire-spool and a graduated plungerbar

hairpin shaped wire are looped through a hole at the tip of the needles for anchorage, the needles are slowly withdrawn. Thus the hairpin shaped Ta¹⁸² wire is introduced precisely into the needle tract. When the legs emerge through the skin, they are bent at a right angle allowing some room for skin swelling. A crossed-end effect is obtained by the bent portion of wire. To minimize personnel exposure, the entire procedure is carried out behind a mobile lead shield. The volume or area of the implant is reconstructed using anteroposterior and lateral roentgenographic projections. Radium dosage tables (Paterson and Parker, or Quimby) are used in dosage calculation after converting the specific activity of Ta¹⁸² to the equivalent activity of radium. In one case (Case vI), a lithium fluoride thermoluminescence dosimeter* was used to verify the calculated dose.

REPORT OF CASES

CASE I. J.E., a 36 year old Negro male, received 6,000 rad for a squamous cell carcinoma of the posterior tongue and 4,000 rad to the left upper neck with a 2 mev. Van de Graaff generator. A month later, he developed excruciating pain in the tongue and marked trismus. Subsequently, he received a 5 day course of intravenous methotrexate† (0.2 mg./kg. of body weight) without appreciable improvement. Tumor invasion of the pterygoid fossa was suspected. En bloc large volume implantation was carried out at the primary site (142 cm.3), left neck (36 cm.2) and left pterygoid fossa (11.5 cm.3) employing Ta182 wire equivalent to 102 mc of radium. A dose of 6,500 rad was delivered in 116 hours to the tongue and neck and the

^{*} Thermoluminescence radiation exposure meter by Madison Research and Development Laboratories, Inc., Middleton, Wisconsin.

^{† 4-}amino-n¹0—methyl-pteroylglutamic acid by Lederle Laboratories, Division of American Cyanamid Co., Pearl River, New York.

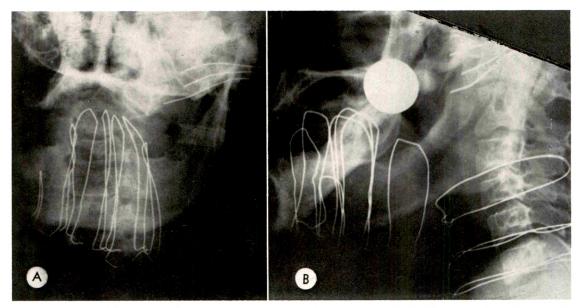


Fig. 2. Case I. (A) Anteroposterior view showing 4 rows of hairpin shaped Ta¹⁸² wires applied percutaneously to tongue, floor of mouth and submandibular area. Three straight wires are seen in the pterygoid fossa. (B) Right lateral view showing a volume implant to primary region and single plane implant to neck.

same dose in 107 hours to the pterygoid fossa (Fig. 2, A and B). The patient experienced almost complete relief from pain after the implantation. He was still free of pain 4 months later when he died of distant metastases.

Comment. In this case excellent palliation of pain was obtained. Local disease was controlled for 4 months.

CASE II. P.G., a 48 year old white male, received 7,000 rad for a squamous cell carcinoma of the left floor of the mouth by radium needle implant and 6,000 rad to a lesion in the left pharynx by external beam therapy in 1956. A recurrent lesion in the left pharynx was intermittently cauterized and irradiated with an additional dose of 1,000 rad by a cobalt 60 unit in 1962. Two years later, he developed a large recurrent lesion in the right posterior tongue. Further irradiation by means of external beam was considered unfeasible and surgical extirpation impracticable. After a 5 day course of intravenous methotrexate administration, the patient underwent a volume implantation (62 cm.3) utilizing Ta182 wire equivalent to 41.95 mc of radium (Fig. 3, A and B). This procedure was performed under local anesthesia. A dose of 6,500 rad was delivered in 116 hours. The tumor volume decreased but the pain and

swallowing dysfunction persisted. He underwent a 5th and 9th cranial nerve section.

Comment. Subjectively, treatment was a failure although the tumor regressed objectively.

CASE III. A.I., a 60 year old white male, was treated for a squamous cell carcinoma of the left floor of the mouth in 1957 by external beam radiation and interstitial radium implantation. Seven years later, he developed a lesion of the same histology in the undersurface of the right tongue. A single plane implantation of an area of 4 cm.² was carried out with 5.65 mc radium equivalent Ta¹⁸² wire (Fig. 4A). The patient received 6,000 rad in 149 hours. The patient is alive and well 5 months after the implantation (Fig. 4B).

Comment. The lesion was thought to be another primary carcinoma arising at a margin of the previously treated area. Technically this was an easy implantation. The patient is well for 5 months.

Case IV. J.C., a 54 year old white male, received 3,000 r with a 250 kv. unit and 3,500 rad by interstitial radium implantation for a squamous cell carcinoma of the left floor of the mouth in 1959. One year later, he developed a

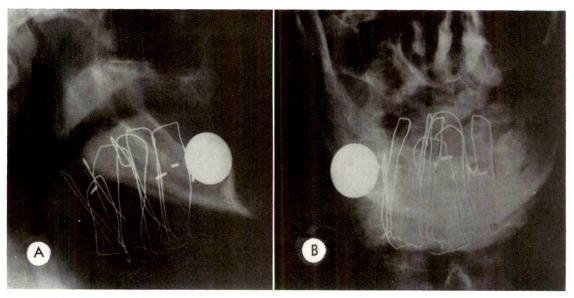


Fig. 3. Case II. (A) Left lateral view showing percutaneous volume implant, using hairpin shaped wires. (B)

Anteroposterior view showing 4 rows of hairpin shaped wires.

palpable neck lymph node and underwent a left radical neck dissection. Four years later, he returned with an ulcerating lesion, 2.5 cm. in diameter, in the right floor of the mouth (Fig. 5C). He received an exposure dose of 3,500 r with an intraoral cone technique (250 kv. unit). This was followed by a Ta^{182} wire biplane implantation of an area of 10.5 cm.² with a separation factor of 1.5 cm. (Fig. 5, A and B). This implantation was successfully carried out through the percutaneous route. He received

6,000 rad in error; the planned dose was 3,000 rad. The tumor regressed completely, but he gradually developed a chronic ulcer in the area of the implantation which required surgical debridement.

Comment. Overdosage was deplorable in this case.

Case v. G.T., an 18 year old white male, presented a 6 month history of squamous cell carcinoma of the right lateral border of the

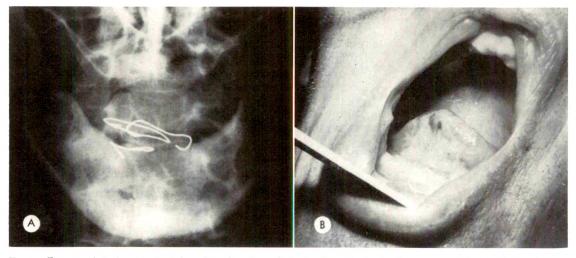
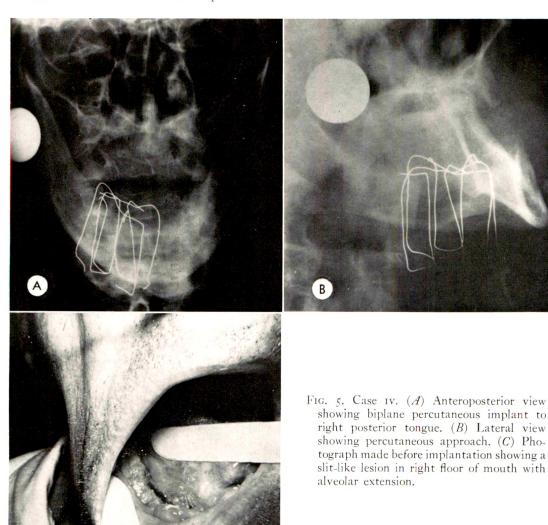


Fig. 4. Case III. (A) Anteroposterior view showing a hairpin shaped wire in the center with 2 straight wires at each end. (B) Right undersurface of tongue. Some mucositis is present but no tumor.



tongue. After receiving 4,400 rad with a 2 mev. Van de Graaff generator, the tumor regressed by over 25 per cent. Two weeks later, a biplane implantation was performed of the tongue (9.54 cm.²), utilizing 18 mc of radium needles to deliver 5,500 rad to the midplane in 75.3 hours. In the ensuing month, the tumor regressed completely, but submandibular induration became apparent. Needle biopsy of this region revealed infiltrating squamous cell carcinoma. Radical neck dissection was completely ruled out. A month later, as a last resort, a volume implantation was carried out percutaneously of the submandibular region, including the floor of the

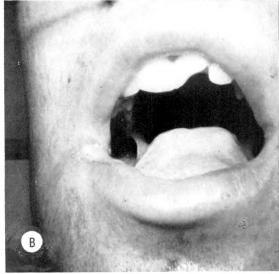
mouth and tongue (Fig. 6A). A single plane implantation was added to the right upper neck (Fig. 6A). The total amount of Ta^{182} wire used was equivalent to 100 mc of radium. Satisfactory tumor regression took place in a month (Fig. 6, B and C). He died of diffuse distant disease 3 months later. Autopsy revealed generalized metastases but no apparent tumor in the primary site.

Comment. This patient followed a rapid downhill course. Grossly, no tumor was seen in the tongue at autopsy.

CASE VI. P.D., a 74 year old white male,



Fig. 6. Case v. (A) Left lateral view showing percutaneous volume implant to right tongue and single plane implant to neck. (B) Mucositis is present but no tumor. (C) After implantation, moist epidermitis is demonstrated but no tumor.



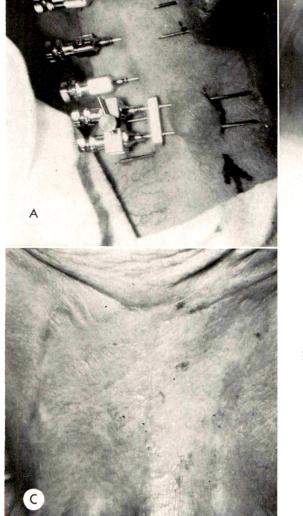


underwent a right hemiglossectomy and a right radical neck dissection for a squamous cell carcinoma of the right tongue. Subsequently, he developed multiple tumor nodules at the operative site. After receiving a 5 day course of methotrexate, he underwent a single plane implantation of the right neck (70 cm.2) under local anesthesia. Ta¹⁸² wire equivalent to 28.45 mc of radium was used (Fig. 7, A and B). A dose of 5,800 rad was delivered in 189 hours to a point 0.5 cm. distant. The tumor dose was confirmed by in vivo dosimetry, using a lithium fluoride thermoluminescence dosimeter. Four months later, while the local tumor was still under control (Fig. 7C), he died of pulmonary metastases.

Comment. Excellent local control was obtained in this case.

DISCUSSION

Ta¹⁸² wire has been in use in interstitial therapy for many years. ^{1,3,8,9,10} It was reported particularly useful in bladder carcinoma. ^{9,10} With the possibility of improving existing methods of Ta¹⁸² wire implantation, we developed a technique of the percutaneous application of Ta¹⁸² wire by introducing a guiding-needle system (Fig. I, A and B). A specially built lead jig was found useful in expedient fabrication and



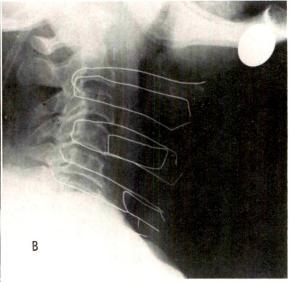


Fig. 7. Case vi. (A) Guiding-needles in place; 2 tumor nodules are demonstrated. (B) Wires in place. (C) After implantation, some epidermitis is present but no tumor.

safe delivery of the hairpin shaped wire of the desired size. Personnel exposure was greatly minimized by a mobile lead shield. This technique was satisfactorily applied to 4 patients under local anesthesia. Case 1, who had an advanced lesion, experienced complete relief from pain for 4 months, when he died of distant disease. Additional palliative measures were required in Cases 11 and 1v due to lack of symptomatic relief. Disease was controlled successfully in Case 111. Excellent local control was obtained in Case v1 for 4 months, when he

died of pulmonary metastases. Case IV had a rapid downhill course and all efforts ended in total failure.

With careful planning and proper selection of wire strength, a volume or area in any dimension can be implanted complying with Paterson and Parker's rule. The percutaneous approach was particularly useful in carcinoma of the tongue and floor of the mouth. This technique is also applicable to lesions in the tonsillar fossa, lateral pharynx, soft tissue and female genital organs.

SUMMARY

An improved technique of Ta¹⁸² wire implantation through a percutaneous route is discussed. This technique was used in 6 patients who had recurrent or extensive lesions in the head and neck area. Ta182 wire implantation was carried out as an adjunct to external beam therapy, chemotherapy or radium needle implantation. New instruments, such as a lead jig, guiding-needle, needle-holder, and space-maintainer are described. This technique was satisfactorily tried in 4 cases under local anesthesia. Disease was successfully controlled in I case. Local disease was controlled in 3 cases for as long as 4 months, when the patients succumbed to distant disease. Adequate palliation was not obtained in 2 cases, one of which was a result of overdosage. Expediency of the technique and adequate shielding minimized the exposure hazard. This technique was found satisfactory in encompassing a complex tumor volume in areas inaccessible otherwise. We feel strongly that the inclusion of this technique is a valuable addition to the existing therapeutic armamentarium.

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INTRACAVITARY RADIATION THERAPY OF CANCER OF THE UTERINE CERVIX BY REMOTE AFTERLOADING WITH CYCLING SOURCES*

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R EMOTE afterloading with cycling sources¹⁰ has been proposed as a solution to the problem of radiation exposure of personnel in intracavitary applicator therapy. In this paper an attempt is made to analyze the usefulness of this principle in the treatment of cancer of the uterine cervix by considering the following questions:

(1) How serious is the radiation exposure problem in intracavitary applicator therapy of cervix cancer? (2) Can replacement of intracavitary radium and radioisotope applicators by external roentgen therapy be advocated? (3) Can radiation exposure from intracavitary applicators in the therapy of cervix cancer be eliminated?

I. HOW SERIOUS IS THE RADIATION EXPOSURE PROBLEM IN INTRACAVITARY APPLICATOR THERAPY OF CERVIX CANCER?

Table I shows as an example of the radiation safety problem in cervix cancer therapy the exposure rates for an applicator loaded with 70 mg. of radium. This amount, used in many clinics, produces at I meter distance a dose rate of approximately 60 mr/hr. in air. For radium, cobalt 60, and other high-energy gamma emitters, the radiation absorption in tissue is nearly compensated for by the scattered radiation. Thus, a radium or cobalt 60 source in a patient causes essentially the same radiation exposure to hospital personnel as a completely unshielded source.

A dose rate of 60 mr per hour or 1 mr per minute at 1 meter increases to 10 mr per minute at a distance of 33 cm., or about 1

TABLE I

RADIATION EXPOSURE IN UTERUS CANCER
TREATMENT WITH AN INTRACAVITARY
APPLICATOR LOADED WITH
72 MG, RADIUM

60 mr/hr.	at 1 meter
I mr/min.	at 1 meter
10 mr/min.	at I foot

10 mr is weekly permissible exposure for nonradiation worker.

foot. One foot is a common working distance for a nurse taking care of a patient with an intracavitary applicator. Although the total body radiation is much lower, a film badge or other dosimeter worn by the nurse would at a distance of 1 foot register the weekly permissible dose for a "nonradiation worker" in only 1 minute time. Even for a "radiation worker" (for whom the permissible dose is 10 times higher), the weekly permissible dose would be registered under these conditions in 10 minutes.

The fact that most physicians and nurses who have treated cervix cancer with radium in the past have not suffered obvious radiation damage has in many institutions fostered an easy going attitude toward the radiation safety aspects of radium therapy for cervix cancer. Enactment of legislation for "permissible doses" has now made safer handling of radium in cancer therapy mandatory in many countries, but the practices of radiation protection still vary widely. We found the most sophisticated armamentarium in Japan, where the awareness of radiation damage as well as the

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technical competence is high. To provide similar facilities, however, is prohibitively expensive in most countries.

Unfortunately, attempts to improve radiation protection often create exaggerated fears and new anxieties. Pinning a film badge on a nurse caring for a radium patient, for instance, is not infrequently equated with a potentially dangerous level of radiation exposure. We have even encountered employees who refused to work in an area where the radiation level is higher than the natural background radiation, though the actual exposure would have been far below the level of 10 mr per week permissible for the general public.

It has been pointed out that the true danger from radiation exposure for hospital personnel is small indeed and that, for instance, the danger of contracting infection is a much greater threat to the health of hospital personnel. This argument, while perfectly valid, cannot alter the fact that not only the public but also the official agencies are today so concerned about radiation hazards that eventually all procedures with significant radiation exposure of personnel will be eliminated.

We must, therefore, conclude that radiation exposure in intracavitary application therapy of cervix cancer, while perhaps not a serious hazard, is indeed a serious problem.

2. CAN REPLACEMENT OF INTRACAVITARY RADIUM AND RADIOISOTOPE APPLICATORS BY EXTERNAL ROENTGEN THERAPY BE ADVOCATED?

External radiation therapy can be used to treat cervix cancer without radium applicators either in form of transvaginal roentgen therapy with special vaginal cones or external roentgen therapy exclusively.

Transvaginal roentgen therapy was already used before radium became available.^{1,2} The older literature is reviewed in del Regato's⁴ paper. del Regato also reported⁵ the only series known to us in which transvaginal cone roentgen treatments

were substituted for intracavitary radium therapy in all treated patients. Following an 8 weeks' course of external roentgen therapy to the pelvis delivering a tissue dose of approximately 2,500 to 3,000 r, he gave by intravaginal cone 4,000 r in 11 days at the level of the cervix using 140 kv. at 25 cm. focus cervix distance. Of 191 patients so treated from 1943 to 1946, 60 or 31 per cent were alive and well at 5 years. The 5 year cure rates by stage were: Stage 1, 14/25 (56 per cent); Stage 11, 23/65 (35 per cent); Stage 11, 16/51 (31 per cent); and Stage 1v, 7/50 (14 per cent).

For purposes of comparison, one may use the figures of the IX Annual Report for the years 1943-1947. It contains data on 29,731 patients from 69 clinics. The overall 5 year recovery rate at all these clinics was 11,392/29,731 = 38.3 per cent. The 5 year recovery rates by stage were: Stage 1, 3,546/5,621 = 63.1 per cent; Stage II, 5,206/ 11,831 = 44.0 per cent; Stage III, 2,461/ 10,113 = 24.3 per cent; and Stage IV, 179/ 2,160=8.3 per cent. For the intravaginal therapy series, the over-all recovery rates as well as those for Stages I and II of del Regato are therefore below the rates from the Annual Reports. However, as the del Regato series is small, the statistical uncertainty of this comparison is great.

Comparison of the dose levels and of the dose distribution of transvaginal roentgen therapy and of intracavitary applicator therapy reveals that with transvaginal roentgen therapy: (1) the dose to the cervix is lower; in del Regato's series, only 4,000 r was given, while with radium applicators doses in the range of 15,000 r to 30,000 r are commonly delivered; and (2) the dose to the parametria is less. Since many cancers of the cervix are not eradicated with doses in excess of 10,000 rads and since parametrial spread of cervical cancer is common and may occur early, intracavitary applicators appear to be superior.

The value of transvaginal roentgen therapy in large exophytic primary lesions, in some cervical stump carcinomas and

in some central recurrences is not disputed.^{3,16} However, it does not appear as a suitable substitute for intracavitary radium applicator therapy for most patients with cervix cancer.

External roentgen therapy alone has not been used for the treatment of cervix cancer in any significant series of patients known to us, but deductions on the relative roles of intracavitary and supplementary high voltage therapy can be attempted on the basis of a randomized clinical trial which was reported by Paterson and Russell. 4 From 1957 until 1961, 703 patients in Stages 1 and 11 were treated with intracavitary applicators. Of these, 363 patients were randomly assigned to receive supplementary roentgen therapy with 2,500 rads kilovoltage or with 3,000 rads megavoltage at Point B. In their report, the whole of the 1957, 1958 and the first 6 months of the 1959 material is analyzed at 3 years. Table 11 shows the 3 year survival rates for 453 patients, 231 of whom were randomly assigned to receive roentgen therapy. These were in Stage 1, 85.6 per cent with and 87.2 per cent without roentgen therapy, and in Stage 11, 57.4 per cent with and 60.4 per cent without roentgen therapy.

No clinical trial was conducted on the

relative importance of intracavitary and roentgen therapy in Stages III and IV of cervix cancer. However, Paterson and Russell also provide some pertinent data on this question, which we have listed in the lower part of Table 11. In 1943-1945, during World War II, Paterson treated 295 Stage III cervix cancer patients with intracavitary applicators, but without external roentgen therapy. The 5 year survival rate of this group was 33 per cent. In the subsequent postwar years, 1946-1949, he treated 490 Stage III cervix cancer patients with intracavitary applicators and with supplementary external roentgen therapy; this resulted in a 5 year survival rate of 40.1 per cent. From these figures for Stage III, results appear better with adjuvant roentgen therapy, but it is noted that as many as 82 per cent of the patients surviving 5 years may be calculated to survive without adjuvant roentgen therapy in Stage III.*

With these data, we have attempted (in Table III) to estimate how many patients with cervix cancer would survive 5 years if intracavitary radium without external roentgen therapy were used in all stages. The XIII volume of the "Annual Report on the Results of Treatment in Carcinoma

* A detailed comparison of the results of the Manchester Clinic with other clinics is to be given in another paper.

TABLE II PATERSON AND RUSSELL'S FIGURES ON 3 AND 5 YEAR SURVIVAL RATES IN CERVIX CANCER WITH AND WITHOUT ADJUVANT ROENTGEN THERAPY*

		Adjuvant Roe	ntgen Therapy	70° 6.0°)	
		With	Without	Type of Study	
Stage I	3 year survival rate	85.6%	87.2%	Prospective Clinical Trial	
Stage II	57 • 4%	60.4%	1957—July 1959 (453 cases)		
Stage III	5 year survival rate	40.1%	33%	Retrospective Analysis Postwar years 1946–1949 (490 cases) vs. World War II years 1943–1945 (295 cases)	

Source: Clin. Radiol., 1963, 14, 17.

* In a communication at the UICC in Mexico City in February 1964, Paterson gave for the same group the following 5 year figures

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* In a communication at the UICC in Mexico City in February 1964, Paterson gave for the same group the following 5 year figures with adjuvant roentgen therapy: Stage 1, 77 per cent, Stage 11, 51 per cent; without adjuvant roentgen therapy: Stage 1, 74 per cent, Stage 11, 53 per cent.

of the Uterus," reports on 116 cooperating clinics for the years 1953 to 1957 with a total of 67,806 patients with cancer of the cervix. Of these, 61,776 or 91.1 per cent were treated and 29,962, referred to in the Annual Reports as apparent 5 year recoveries, were alive with no evidence of disease at 5 years. This is 44.2 per cent of all patients examined and 48.5 per cent of all patients treated. In this group 11,372 or 37.95 per cent were (as shown in column A of Table III) in Stage 1; 12,364 or 41.27 per cent in Stage II; 5,935 or 19.81 per cent in Stage III; and 291 or 0.97 per cent in Stage IV. If one multiplies these figures with the corresponding data from Paterson and Russell (Column B taken from Table II) and if one credits all cures in Stage IV to external radiation therapy, one comes to the conclusion that 95 per cent of all 5 year cures during this period could have been achieved by intracavitary therapy alone. We have carried out the same analysis for the XII Annual Report, which covers the years 1950 to 1954 and found that in this case, 96 per cent of all 5 year cures during this period could have been achieved by intracavitary therapy alone.

One must not, of course, infer that external roentgen therapy would give a 5 year survival rate of only 5 per cent. Undoubtedly, the figure would be much high-

er, since a number of cervix cancers are radiosensitive enough to be cured by doses which can be delivered safely by external radiation therapy.

In some hospitals, cervix cancer patients are now treated exclusively by external radiation therapy, and it will be interesting to see the results in these series. While we are not against carefully controlled clinical trials on the value of exclusive external radiation therapy in cervix cancer in clinics with appropriate staff and facilities, we feel that it is not justified at present to advocate replacement of intracavitary radium and radioisotope applicators with external radiation therapy.

3. CAN RADIATION EXPOSURE FROM INTRACAVITARY APPLICATORS IN THE THERAPY OF CERVIX CANCER BE ELIMINATED?

Figure 1 shows "afterloading" for uterus applicators, which we introduced in 1960 in an effort to find a solution to the radiation safety problems associated with the use of intracavitary applicators. Improved models of our uterus afterloading applicators have been described in subsequent publications.^{8,9}

The first step is the insertion of an unloaded applicator in the operating room. In this applicator, the vaginal and uterine

Table III

ESTIMATE OF THE PER CENT OF CURABLE PATIENTS WITH CERVIX CANCER WHICH COULD BE CURED BY INTRACAVITARY APPLICATORS WITHOUT SUPPLEMENTARY EXTERNAL ADJUVANT ROENTGEN THERAPY

Stage	A Per Cent Contributions to Total No. of 5 Year Cures*	B Paterson and Russell Data on Results without Supplementary Roentgen Therapy†	C (A×B) Per Cent of All Patients Which Could Be Cured without External Roentgen Therapy
I	38% 41%	1∞% 1∞%	38% 41% 16%
III IV	20% 1%	82% —	16% —
All Stages	100%		95%

^{*} XIII Annual Report (Stockholm 1964).

[†] Paterson and Russell, Clin. Radiol., 1963, 14, 17.

parts are connected to 3 tubes, which protrude from the vagina. Roentgenograms of the inserted applicator loaded with dummy sources are then taken to determine if the position is satisfactory. After the patient is in a single room, the radioactive sources are introduced into the uterine and vaginal portions of the applicator.

With afterloading, radiation is eliminated in the operating room, in the recovery room, in the Diagnostic X-ray Department and in the hospital areas through which the patient is transported. These obvious advantages have led to rapid acceptance of afterloading for uterus applicators. 6,12,15,18,19

We thought originally that this after-loading technique provided a sufficient improvement in radiation safety. However, we found that the remaining radiation exposure of the physicians, nurses and other personnel still caused many complaints and problems and believe now that every effort should be made to eliminate the remaining radiation exposure from intracavitary applicators. In principle, this is possible by "remote afterloading", which has been used for small teleradium bombs for more than 25 years¹⁷ and is widely applied in industrial



Fig. 1. Simple afterloading of uterus applicators.

radiography with gamma-ray sources. However, the design for a remote afterloader for intracavitary applicators presents considerable difficulties, because many sources of different active lengths and loading patterns are required.

A solution to this problem was found by using small sources of high activity and cycling them back and forth slowly during the treatment, as is illustrated in Figure 2.¹⁰ By changing the length of the cycling movement and by programming the speed of the source movement, sources of any active length and of any loading pattern may be simulated. In our experience, 3 sources of identical activity and cyclic movements up to 15 cm. appear sufficient for remote afterloading of all commonly used intracavitary applicators.

In use, an unloaded uterus applicator is

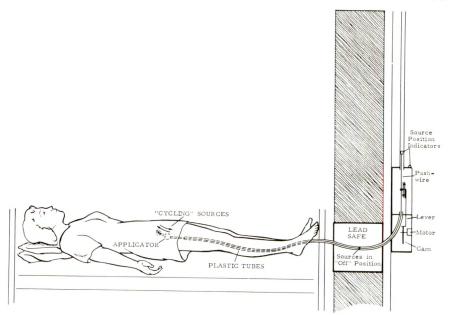


Fig. 2. Remote afterloading of uterus applicators with cycling sources.

inserted first. The patient is then placed in a shielded room. The uterus applicator is connected with 3 plastic tubes to a leadshielded safe in the wall. This safe contains 3 small sources of high activity, which are attached to the end of 3 cables. From the control panel outside the room, the sources are now pushed into the uterus applicator. The two vaginal lateral sources ordinarily remain stationary during the treatment. The uterine source is cycled (slowly back and forth) by an electrical motor drive over the desired length. Since this can simulate sources of any desired length and loading pattern, no additional sources are required, no special radium storage room is needed, and no transport of sources is necessary. Further, no bookkeeping is required for the radioactive sources. All major causes of past radium accidents are therefore removed.

With this remote cycling afterloader, the radiation from the intracavitary applicator is confined to the treatment room, provided it is well shielded. Much stronger sources may therefore be used and treatment can be given in very short times. This would permit treatment with intracavitary applicators on an outpatient basis. It also makes it possible to use special positions, such as the Trendelenburg position, alteration of the oxygen pressure during treatment, cooling of the rectum and the bladder, and other measures designed to improve the therapeutic ratio.

If shorter treatment times are used, one should employ greater fractionation, since it is well known that for a single intracavitary or interstitial application, shortening of the duration of the treatment time lessens the selective effect on the cancer and causes more complications. However, the experience with the "Stockholm technique" (2 short applications of 1 day each) and of the "Paris technique" (I continuous application of 7 days) have shown that for intracavitary applicator therapy of cervix cancer, fractionation can be used in place of protraction. In considering this question, one should bear in mind that in roentgen therapy, treatment of patients over a long

period during each session was at one time also strongly favored (Coutard's protractedfractionated radiation therapy). This practice was abandoned because strikingly better results were not forthcoming.

On the basis of our limited experience in the last years with cervix, nasopharynx, and esophagus cancer treated with strong sources in a few hours, we prefer for treatment of cancer of the uterine cervix 3 applications, each at least 2 weeks apart. Comparative clinical trials on short versus long treatment times are necessary, however, before definite recommendations can be made.

As radiation sources, all natural and artificial radioisotopes can be employed which have been used in the past for intracavitary applicators. If long half lives are desired, radium 226 and cesium 137 are the first choice. However, if one wants to use very short treatment times, cobalt 60 and iridium 192 sources become preferable, because they can be produced in much higher specific activities. In the choice of a source, one must also consider that much less room shielding is required for cesium 137 and iridium 192 than for radium 226 and cobalt 60.

SUMMARY

1. The high activity sources required for radiation therapy of cervix cancer with intracavitary applicators make satisfactory radiation protection of personnel difficult and costly.

2. Intracavitary radiation therapy is essential for cervix cancer treatment and no satisfactory evidence is available to show that the same results can be accomplished by transvaginal or external roentgen therapy.

3. Radiation exposure of personnel from intracavitary sources can be completely eliminated in intracavitary radiation therapy by the use of a remote afterloader with cycling sources.

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CERVICOVAGINAL IRRADIATOR—A TRIPLE APPLICATOR

By WALTER P. SCOTT, M.D.

THE applicator* which is described is fundamentally a vaginal irradiator; nevertheless, it does lend itself well to disease of the cervix and cervical stump, especially in situations where the pelvic anatomy precludes the use of ovoids (colpostats). It also serves quite well in managing involvement of the vaginal cuff and in prophylactic irradiation of the vault, e.g., endometrial carcinoma. This cervicovaginal irradiator evolved as a result of experience gained with primary, secondary, and "prophylactic" cervicovaginal situations with the three basic radium methods: (1) radium plaque, (2) vaginal tandem arrangements, e.g., ovoids, cylinders, etc., and (3) low intensity radium needle implantation. Thus, the cervicovaginal irradiator combines the features and advantages of these techniques, consolidating them into a single unit which will accommodate most any situation to give unlimited possibilities of radiation distribution (Fig. 1, A, B and C; and 2). Needless to say, each method may be used independently in combination with the others, thus rendering infinite versatility. Rather than rely on heavy lead inserts, I depend upon distance (inverse square law) to protect the uninvolved structures. By building up the radiation in the peripheral zones with low intensity needles, the dosage in the central zone may be reduced accordingly. The needles in the plaque may be so arranged as to concentrate and limit the radiation to the involved area or sector of disease and/or serve to "cross" the ends of the low intensity needles within the cylinder. Thus, the applicator lends itself quite well to the Paterson-Parker technique of dosage calcula-

MATERIAL

Figure 1A is a diagram showing the cervicovaginal applicator. At the top is the plaque with 4 grooves that can accommodate either low or high intensity needles and 2 small tenaculum holes in its side. In the *center* is the cylinder, varying in length according to the low intensity radium on hand—I use lengths of 45, 61, 73 mm. in order to accommodate the 44 mm., 60 mm., and 28 mm. (plus 44 mm.) low intensity needles within the 12 peripheral channels set at I through 12 o'clock. The central channel is bored to accommodate whatever radium elements are available, e.g., capsules, needles, tubes, tandems, etc. The transverse channel is placed in the external end of the cylinder and set at right angles to the 12 o'clock—6 o'clock axis. A suture passes through this and secures and stabilizes the cylinder within the vaginal canal. An alternate model (not shown) has transverse suture channels at every 30 degrees, in which case the cylinder rather than the plaque is rotated in order to line up the needles within the plaque. Applicator diameters of 3.0 cm. to 3.5 cm. will usually handle most situations. A 3.0 cm. plaque will accept 5 mg. needles and a 3.5 mm. plaque, both 5 mg. and 10 mg. needles. Diameters of less than 3.0 cm. will not, for all practical purposes, take advantage of the inverse square law. The cap to secure needles and elements within the cylinder is shown at the bottom of Figure 1 A. This also has two small tenaculum holes in its side.

SPACE-DOSE RELATIONSHIP OF VARIOUS LOADING ARRANGEMENTS

The space-dose relationship of various loading arrangements is shown in Figure

Row A. Basic loading possibilities of

^{*} Cervicovaginal Irradiator—A Triple Applicator: Radium Chemical Co., New York.

CERVICO-VAGINAL IRRADIATOR - A TRIPLE APPLICATOR

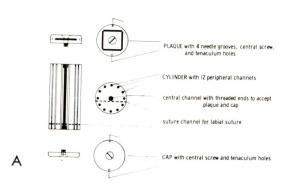
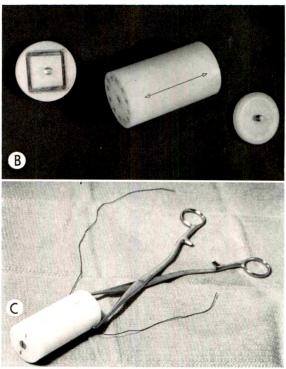


Fig. 1. (A) Cervicovaginal irradiator — a triple applicator. (B) The unassembled applicator. (C) The assembled applicator.



plaque and cylinder. High (5 mg. and 10 mg.) intensity needles within the plaque irradiate the (uterine) structures above while low intensity needles within the plaque serve to "cross" the ends of the low intensity needles below. The central channel of the cylinder may be loaded with high intensity elements, low intensity needles, or left empty. The 12 peripheral channels are to be loaded with low intensity needles.

Row B. Completely loaded system for irradiating the cervix, cervical stump, vaginal cuff, and/or vaginal vault.

Row C. Suggested loading for irradiating the vaginal walls—ends are crossed with low intensity needles within the plaque. If desired, a second plaque may be used to cross the other ends of these needles. With high intensity elements within the cylinder, the entire vaginal vault may be irradiated with augmented dosage to the vaginal walls and diminished dosage to the rectum and bladder.

Row D. Loading of a 180 degree vaginal sector sufficient to cover a 120 degree sector of disease within.

TECHNIQUE

The ready and available tenaculum may be used to manipulate all three components by virtue of the small transverse tenaculum holes in the cap and plaque and the suture channel passing through the cylinder. The technique is as follows:

- 1. Measure the vaginal vault with the correct size applicator.
- 2. Load the plaque.
- 3. Attach the cylinder to the plaque and with the cylinder in the 12 o'clock high position, rotate the plaque to give the needle alignment desired.
- 4. Pass a suture through the transverse channel in the cylinder, introduce the cylinder into the vaginal vault, and then pass one end of the suture through the left labium majus and the other through the right labium majus in order to stabilize the cylinder.
- 5. Load the central channel with high intensity elements and/or the appropriate peripheral channels with low intensity needles.

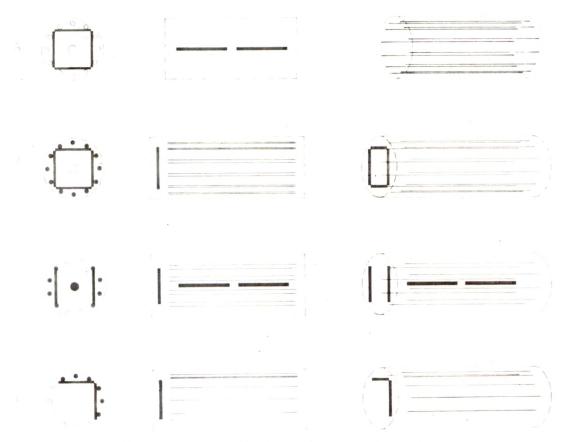


Fig. 2. Space-dose relationship of various loading arrangements.

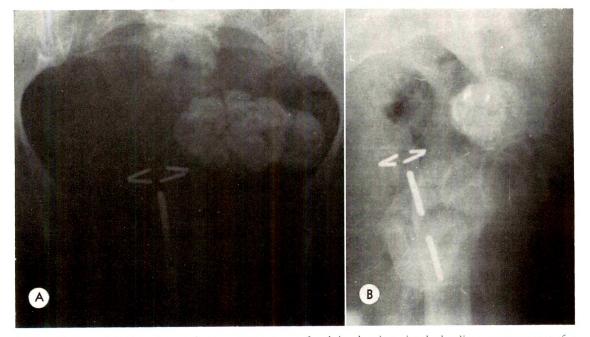


Fig. 3. Case i. (A) Anteroposterior roentgenogram of pelvis showing simple loading arrangement for prophylactic irradiation of vaginal vault. (B) Lateral view.

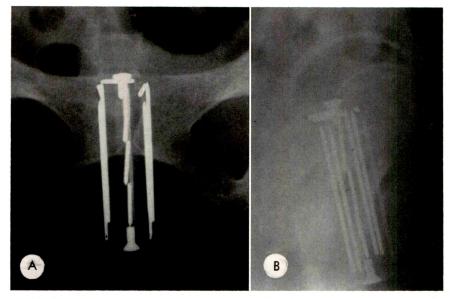


Fig. 4. Case II. (A) Anteroposterior roentgenogram of pelvis showing loading for anterolateral vaginal wall metastatic disease. (B) Lateral view.

- 6. Attach the cap which secures the needles within the cylinder.
- 7. Tie the ends of the sutures together.

ILLUSTRATIVE EXAMPLES

CASE I. Figure 3, A and B illustrates the case of a 71 year old white female with Stage 1 adenocarcinoma of the endometrium. This patient has completed irradiation of the uterine cavity with Heyman capsules and the applicator is used for irradiating the vaginal vault. The applicator arrangement is the simplest type for prophylactic irradiation. It can be noted that the 4 high intensity needles within the plaque form a square which is rotated 45 degrees in order for its angles to point at 12, 3, 6 and 9 o'clock. In this manner, the rectum and bladder are receiving minimum radiation, yet the whole cervicovaginal area is receiving homogeneous radiation which is supplemented by the high intensity elements within the central channel of the cylinder.

Case II. Figure 4, A and B illustrates the case of a 56 year old white female who has recently completed telecobalt 60 radiation therapy for squamous cell metastatic vaginal disease 2 years following treatment for carcinoma of the

cervix. The applicator was loaded somewhat similar to the arrangement shown in Figure 2 (Row C) but with an added (third) 5 mg. radium needle in the anterior groove of the plaque, three—10 mg. needles within the central channel, and five—3 mg. needles at 8, 10, 12, 2 and 4 o'clock to augment the dosage to the residual disease of the anterolateral vaginal walls, thus sparing the rectum.

SUMMARY

No other malignant condition requires more individualization than carcinoma of the vagina. Invariably, more than one, and often two modalities are called upon and quite frequently more than one radium technique is employed. The cervicovaginal irradiator described consolidates these techniques into a single unit, namely plaque, tandem, and low intensity needle, which is mechanically simple, inexpensive, and lends itself well to the Paterson-Parker system for dosage calculation.

Department of Radiotherapy Charlotte Memorial Hospital Charlotte, North Carolina

AN UNFAVORABLE ENCAPSULATION EXPERIENCE WITH SCREWED-TIP RADIUM SHEATH NEEDLES*

By CASSIUS M. CLAY, S.M., MARK BROWN, M.D., and HAROLD S. ENGLER, M.D. AUGUSTA, GEORGIA

SINCE 1957, our Department of Radiology has had 3 unfavorable encapsulation experiences with the same group of screwed-tip, gold alloy radium sheath needles. In each case, failures were detected before widespread radium contamination occurred, but the number of episodes has been frequent enough that institutions or radiologists using such needles should give serious consideration to a more secure form of encapsulation.

NUMBER AND TYPE OF NEEDLES INVOLVED

The radium needle inventory under discussion includes 45 different sheath needles varying in radium content from 1.7 mg. to 2.7 mg. These needles contain a total of 128 inner radium cells loaded such that the resultant activity is either 0.33 mg. per cm. or 0.66 mg. per cm. All the needles are similar in construction and were fabricated in late 1956. Each gold alloy sheath contains one or more platinum-iridium encapsulated radium cells within its hollow core. One end of the needle is permanently closed and drilled to form a needle eve. This end lacks the usual stylet hole for facilitating the removal of cells. The other end is open and has internal threads. A trocar-shaped gold-alloy tip with external threads is screwed into the open end to close it and keep the radium cells from falling out. Details of this construction, as commercially distinguished from permanently soldered European or American type platinum-iridium needles, are shown in Figure 1. The 128 inner radium cells loaded into the sheath needles were certified by the manufacturer to contain only radium sulphate co-precipitated with barium sulphate and to have been freshly encapsulated and leak tested in late 1956.

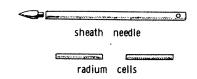
EXPERIENCE WITH LEAK TESTS

The 45 sheath needles were placed in

removable trocar tip
loose radium cells (0.2mm thick
platinum-iridium walls)
eye

screw threads
tubular sheath (0.4mm thick
gold-alloy walls)

CROSS - SECTIONAL VIEW - NOT TO SCALE



PICTORIAL VIEW - ACTUAL SIZE

Fig. 1. Construction of a typical screwed-tip, goldalloy radium sheath needle. A 2 cell needle may contain up to 1.33 mg. of Ra²²⁶ as radium sulphate co-precipitated with barium sulphate.

service in February, 1957. Since that time, they have been used for many radium therapy applications but have always been carefully leak tested at least once a year using the glass test tube, cotton absorbent plug and GM tube method discussed by Rose.³ Single needles with minor leaks were discovered in September, 1958 and in April, 1964. These leaks occurred through the interstices between the screw thread joints since none of the tips had ever been removed. Except as protected by their goldalloy sheaths, the two or more inner radium cells that failed and leaked were subjected to neither bending nor other unusual stresses. This incidence of inner cell failure (approximately one leak per 100 inner cells

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every 3 years) indicates that these cells are not a secure form of encapsulation.

THE LOOSE TIP INCIDENT

In January, 1965, inspection of midtreatment roentgenograms taken after a tongue and cheek implant using 8 of the sheath needles indicated that the trocar screw tips on 2 of the needles had loosened and that the tip on the third needle had become completely detached. Figure 2 shows a lateral roentgenographic view of the implant and Figure 3, a close-up of the needles. Notice the arrow pointing to the completely detached tip. Roentgenograms and image intensifier fluoroscopic examination immediately after implantation showed no defects in the needle tips but they did indicate that the needles were subject to considerable motion when the patient moved his tongue. This motion presumably caused some of the tips to become unscrewed by the third day when mid-treatment roentgenograms were taken. As a precaution against inner radium cells slipping out of their sheath, the entire im-

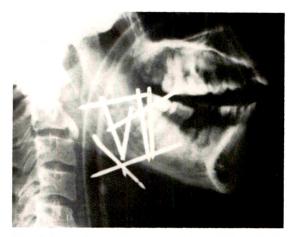


Fig. 2. Lateral roentgenogram of a tongue and cheek implant, showing 3 defective screwed-tip radium sheath needles, taken immediately prior to removal.

plant was removed ahead of schedule from the anesthetized patient in an isolated operating room under radium spill safety procedures.

With the exception of one tip, all needles and tips were recovered. The one detached, inert tip was left in the tongue rather than subject the patient to traumatic explora-

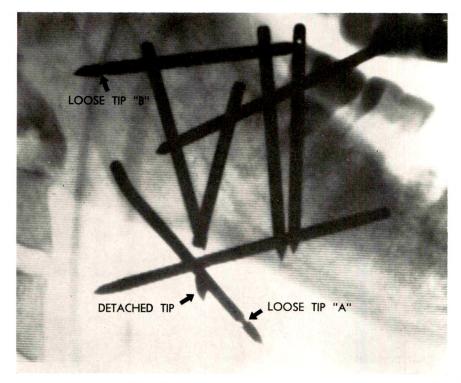


Fig. 3. Close-up roentgenogram. Note the 2 sheath needles with loose tips (A and B). A third needle has completely lost its tip (see arrow).

tion. After removal, the needle without tip and the two needles with loose tips were carefully examined. Fortunately, clotted blood had securely fixed the loose radium cells inside the hollow sheath of the needle that had lost its tip. There was no evidence of a radium leak. In the event a cell had slipped out and remained deep in the tongue, surgical resection of the tumor and the radium cell would probably have been necessary since searching for a small foreign body deep in a tongue is difficult. Prior experience with leak tests in this same group of needles and the experience of others elsewhere emphasized the potential hazards of attempting to recover an unprotected isolated cell. Its thin 0.2 mm. thick wall might have developed a serious leak or rupture when grasped by a forceps or accidentally punctured by a scalpel or probe.

The other 2 needles with partially unscrewed tips apparently had become loosened during or after implantation and were further unscrewed by the motion of the patient's tongue. The threads of all 3 were in good condition and had been routinely checked for tightness with a special wrench prior to use. No radium leakage occurred in connection with the January, 1965 loose needle radium incident but such a possibility existed.

DISCUSSION

In view of the two minor leaks and the loose tip incident all within slightly more than 7 years of use, the entire group of screwed-tip needles were returned to the manufacturer for disassembly and leak testing. After the individual cells were checked and reloaded, the manufacturer's service department silver-soldered the screw tips of the assembled needles to provide greater intrinsic safety. It was decided that the security against lost tips and the gain of double encapsulation4 outweighed the potential advantage of disassembling a sheath needle and reloading it for non-linear dose distribution. Soldering each tip in place will cause the more rigid gold-alloy sheath to form a positive, second hermetic seal and thus supplement the original, solder seals of its inner, thinwalled radium cells. Other types of sheath needles with stylet holes at the eye end can likewise be converted to double encapsulation by soldering both ends. Soldering should not be attempted except under special radiation control conditions.

Because estimates have appeared in the literature that radon, helium and other gases generated by the radioactive decay occurring inside a sealed radium cell may increase its internal pressure approximately I atmosphere per year after encapsulation,2 the addition of a second solder seal in the more rigid needle sheath is expected to reduce the frequency of future leaks. Soldering the threaded joints will also reduce the possibility of implanted needles losing their tips and invoking the hazard of ruptured radium cells.

SUMMARY

Three potentially hazardous experiences with 45 screwed-tip, gold alloy radium sheath needles over a 7 year period are reported. The advisability of permanent double encapsulation is emphasized and a simple method of converting single encapsulated sheath needles is described.

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EVALUATION OF METHODS OF COMPUTER ESTIMATION OF INTERSTITIAL AND INTRACAVITARY DOSIMETRY*

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PATIENTS have long benefited from the information gained from external therapy beam isodose curves and the detailed dose distribution reconstructions that can be obtained from them. The knowledge derived from these dose representations for various therapy modalities, when combined with a critical evaluation of the clinical pattern of tumor extent and the tolerance of normal tissue, has led to studies resulting in optimal treatment dose distribution.

Similar detailed dose information can now be obtained for interstitial or intracavitary treatment. It should, therefore, be possible to combine this knowledge of dose distribution with the improved techniques of source introduction (afterloading sources in flexible tubing), optimal source characteristics (low half value layer sources) and an understanding of the clinical requirements of the implant so as to produce optimal intracavitary or interstitial treatment.

The detailed dose distribution information in the region of applicators or implants is obtained either by computer estimation or by onerous and time-consuming human calculation. Fortunately a number of programs have been developed 1,3,4,6,7 and used in clinical cases to produce rapidly and at low cost an amount of information otherwise unavailable or impractical to acquire. In the programs now available, varied methods are used to get to the same result—useful and meaningful

dose information. Because of the great expense involved in developing the various programs and the repetition of the stages of development in the hands of a number of independent workers and because of the lack of general usefulness of the existing programs to all radiation therapists, it was considered beneficial to determine which program is most effective. An investigation was, therefore, undertaken to evaluate the peculiar benefits of each of the existing programs, to test applicability and validity, and hopefully to lead to ways of developing an ideal program.

CRITERIA OF COMPARISON

We have attempted to compare 4 publicly presented and available programs on the basis of:

A. Accuracy in terms of the relation between the dose calculated for specific points and the actual dose measured at those points. Because of the difficulty in measuring the dose around radioactive sources, a clinical level of accuracy was considered sufficient. In fact, a simple statement of per cent difference between the measured and calculated dose is almost meaningless, since in the region of high dose where the dose gradient is steep, the size and presence of most measuring devices make accurate estimation impossible, and in the region far from the sources where the dose gradient is less steep and the doses low, a small variation that may be due to inadequate sensitivity of the instruments

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appears to be a significant per cent error. A more reasonable estimate of accuracy is the statement of distance the measuring device would need to be moved in order that the measured and calculated doses coincide. In clinical practice, in the case of interstitial implants, the important volume is in the immediate locale of the sources, and variations of even 2–3 mm. may be significant. However, in the case of intracavitary implants, the volume of interest is some distance from the applicator, and the critical distance may be as much as 0.5 cm.

B. Validity of the doses calculated. It is necessary that the dose information obtained contain sufficient detail and concern the doses at critical points. For example, it is necessary to know the dose in the cervix, bladder, rectum, and lymph nodes in the case of a pelvic implant. In these cases, dose presentation regarding the dose at Point A or Point B or any other arbitrary points has very limited value. Similarly, it is superfluous to have too detailed dose information, as it is probable that the applicators move during the course of an implant, thereby changing the dose from that calculated on the assumption of a fixed position of the applicator.

C. Versatility for the program to handle all types of implants. It is reasonable to expect the program to be suited to any of the many types of applications, intracavitary or any of several types of interstitial; of any of a number of types of sources, such as tubes, needles or point sources; and any of a variety of isotopes, for example, radium, Co⁶⁰, Cs¹³⁷, Au¹⁹⁸, Ir¹⁹²; and perhaps combinations of these sources when arrayed in any of the myriad geometric constructions we call an implant.

The program of the Mallinckrodt Institute of Radiology (MIR)⁴ meets this extreme versatility requirement, but for the needs of a single institution, this program may not be required. However, for general applicability, such a program is definitely needed.

D. Economy with respect to the other costs of the patient's treatment. It is unreasonable for the dose determination method for any single case to be more expensive than other more necessary procedures. Since the cost of treatment is already high, considerable emphasis must be put on the effort to keep cost low.

E. Applicability and availability for general use of interested therapists. No program has merit intrinsically, but its usefulness is determined by the contribution made in patient care in a great number of institutions. The value of the computation may lie in the use of the information to modify the implant and in such cases, the information should be rapidly acquired, as it probably has little value for that patient if the calculations are returned following removal of the implant. A further major requirement for general availability and applicability of a program is that the method of input be technically simple. A simple film method of localizing sources is needed and a simple method of obtaining the input data from the films is mandatory. If these requirements are met, then with modern telephone or mail communication, almost any computer center capable and willing to perform the computation is near enough to aid in the clinical problem.

MATERIALS

In order to compare the various programs, 3 available and publicly presented programs were compared with the MIR program for the type of application for which the program was designed. Several other programs have been developed and are in clinical use, but since they have not been reported or presented by their authors and are not publicly available, these have not been compared.

The 3 programs which were compared to the MIR program were presented by: Shalek and Stovall^{6,7} (Program A); Adams, Peterson and Collins² (Program B); and Adams and Meurk¹ (Program C).

The comparison of the various programs

for all criteria other than accuracy has been done on the basis of the published or presented reports of the programs and represents a comparison of the MIR program with the stated characteristics of the 3 comparison programs.

In each case, for an accurate comparison, the authors of the program have communicated to us their program listing, the conventions to be used for input and output, and have given aid and advice when we had problems in translating the program to our equipment.

In the case of Program A, our computer facility is not adequate to handle the program, and the computations which were compared were performed by the staff and computer for which the program was designed.

The computations to be presented for comparison of Programs B and C were carried out with the Washington University computer center facilities and our output data were compared with those of the same problem, solved by the originators of the program. The extreme kindness and consideration shown by the authors of Programs A, B, and C demonstrate the basis of the statement that the programs are available in the truest sense.

Each of the 3 comparison programs presumes the use of radium as the isotope to be implanted and makes no provision for other isotopes that may be used for implants.⁵ Program A can be used with interstitial sources only, and Programs B and C are usable only for intracavitary sources.

COMPARISONS OF ACCURACY

I. Program A Compared with Program MIR for Interstitial Implant. In order to compare these 2 methods, a simple model was built by precisely placing 2 radium needles in a block of lucite (Fig. 1). From the known position of the sources, the coordinates were introduced and the computation was performed for each program. Program A and Program MIR were found to be in quite close agreement for the lower

plane (Program MIR doses converted to rads for the comparison with Program A) and these determinations were in excellent agreement with the measured doses as determined by ionization chamber (Landsverk sealed 10 r chamber) and probe scintillation counting rate meter (anthracene crystal probe counter). At a point 3.3 cm. from the line connecting the needles at the level of the midpoint of the shorter needle, the dose measured in water using an anthracene crystal probe scintillation counter was 2.31 rads/hour. The dose computed by Program A was 2.09 and the dose calculated by Program MIR was 2.42 rads/hour. In neither case, therefore, was the dose significantly different from the measured dose, and in each case a movement of the probe by 2 mm. would produce the computed dose. However, the upper plane of calculation cannot be performed by Program A, as the shorter needle does not pierce this plane of calculation. Since it is not uncommon for some of the needles in an implant not to pierce all of the planes of calculation, the inability to include these needles in the calculation or the inability to calculate the plane appears to be a drawback of the method. We have seen a computation by an excellent new program from the authors of Program A which resolves this problem.

2. Programs B and C and MIR Compared for Intracavitary Implant. The 3 methods were compared by introducing the coordinates for a known implant and computing the dose distribution by each method (Fig. 2 and 3). Representative isodose curves were compared with each other and with the empirical dose determination made previously with an anthracene crystal probe scintillation counting rate meter. A previous comparison of the Program MIR and the empirical doses showed excellent agreement.4 Programs B and C demonstrated excellent dose agreement with Program MIR. In each of the 3 programs, the doses measured at distances greater than I cm. from the implant were in excellent agreement with the

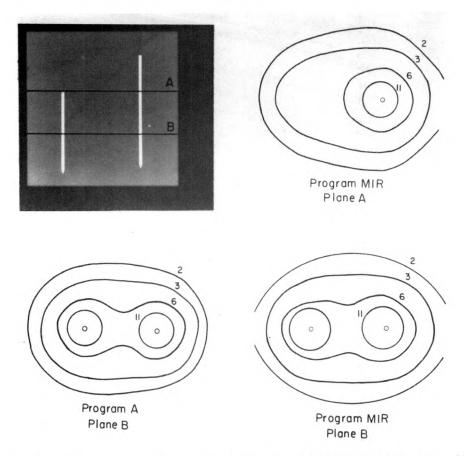


Fig. 1. Comparison of the accuracy of Program A and Program of the Mallinckrodt Institute of Radiology (MIR) for an interstitial implant. Program A is unable to calculate the plane which is not pierced by the shorter needle. The isodose curves on the other plane are almost identical.

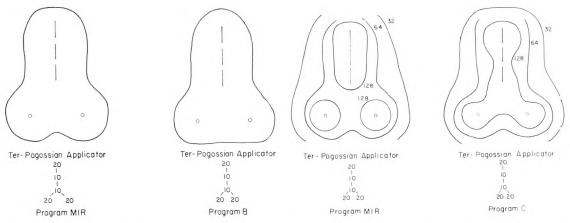


Fig. 2. Comparison of the accuracy of Program B and Program MIR for an intracavitary implant. The two isodose curves are almost the same. No significant variation is seen.

Fig. 3. Comparison of the accuracy of Program C and Program MIR for an intracavitary implant. The isodoses are nearly identical, with no significant variation.

calculated doses by each of the 3 programs and with the empirically determined dose.

COMPARISON OF VALIDITY

In each program, the dose estimation adequately expresses the dose at the critical points in the implant. Program A is far superior in that the density of information (each millimeter) allows a detailed description of the dose pattern. For clinical purposes, the other 3 programs present sufficient data to meaningfully interpret the implant.

COMPARISON OF VERSATILITY

Program MIR is more versatile than any of the other 3 programs, since it is possible to determine dose around a greater variety of implants, including irregular interstitial implants, with associated intracavitary sources. Each of the other 3 programs can be converted to deal with sources other than radium, but none can be easily converted to include irregularly placed sources.

COMPARISON OF ECONOMY

All of the programs are relatively expensive, but since the cost of computer time is rather arbitrarily fixed in various institutions, it is not possible to make a reasonable comparison. While the use of a large computer is more expensive per minute of computer time, each minute produces much computation so that the amount of information derived costs less when determined by a large computer than it does for a small one. The price of each of these computer programs for a typical case would vary between \$20 and \$50. This does not include the tremendous cost of developing the programs. In order to reduce the cost, we have performed computer calculations for a number of varied situations of loading and geometry for the Ter-Pogossian applicator.8 This permits construction of an atlas that aids in treatment planning as well as in making recomputation unnecessary (Fig. 4).



Fig. 4. Diagram of the 3-dimensional model of the Ter-Pogossian applicator, constructed from isodose curves obtained by calculation of doses on 5 planes by Program MIR.

COMPARISON OF APPLICABILITY AND AVAILABILITY

The programs described are each applicable and available to a greater or lesser extent, depending on how much like the prototype is the problem to be solved. Each program closely fits the sources and implant methods of the originating institution. Because we have had a wide variety of problems and were using Co60 and Ir192, we developed the MIR program to accept any type of source, regarding isotope, size, shield, or activity, thus more nearly accepting the possible wide variety of requirements for use. All of the programs are available. Program A is available to a greater degree than the others, as a mechanism has been set-up by which one can mail or telephone in the input data and receive an air-mail reply with the output data in graphic and tabular form. The Washington University has the advantage of computer facilities and inquiries about the use of the MIR program are welcome.

DISCUSSION

This project was originally undertaken because preliminary observations demonstrated a difference of the order of 20 per cent in the comparison of the dose at a given point as calculated by 2 of the programs. Further investigation demonstrated

that such differences exist, but that the distance to be moved for normalization of the dose for the several programs is measured in millimeters. Thus, the programs closely agree in the expression of dose and certainly agree within the clinical expectation of accuracy.

The programs vary considerably in their versatility and, therefore, in their general applicability; however, each program has specific benefits which can be adapted to produce an *ideal* program.

The construction of volume dose distribution models as an atlas of various implants should provide a way of predetermining from the nature and extent of the lesion the type of implant and loading that would be most effective. In the case of the interstitial implant, a model of the desired or possible implant can be constructed, and from this model and computation, the optimum loading can be determined. With an afterloading system, all of these calculations can be related to the actual implant, thereby permitting optimal loading. Even if these mechanisms are not possible, the feedback from the results of an implant (success or failure tolerance or necrosis) and comparison with the dose calculations should be of aid in the planning for other cases.

Only by the computer methods do we get an adequate amount of information about the 3-dimensional distribution of dose to permit reasonable teaching or evaluation of implants. In spite of the considerable experience built up by a number of capable and skilled physicians in the application of radioactive implants, it is difficult to teach the concepts and techniques so that the novice can appreciate in a concrete way the 3-dimensional dose distribution without a computed model. After observing implants and models of their dose representation, it becomes clear that the maxim "at distances from a source equal to or greater than two times the length of the source, the dose variation is nearly approximated by an inverse square function" is nearly true and can be used as

a rapid approximation of dose without the necessity of performing explicit calculations in the estimation of doses from intracavitary applicators. The inadequacy of this "rule" for interstitial implants rapidly becomes evident.

An ideal program would have a simple, rapid, and accurate input; a concise and accurate computation method using reasonable factors and logic; and a clearly meaningful output with application to any type of implant or source. Since the cost of computer determination is mainly in program development, it is reasonable to combine and modify the existing program for general applicability rather than duplicate existing programs.

SUMMARY

- 1. Various existing and publicly available computer programs for interstitial and intracavitary dosimetry were compared.
- 2. All of the programs have adequate accuracy for the clinical problems which they solve.
- 3. Suggestions regarding an "ideal" program are made.

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AN EXPERIMENTAL DETERMINATION OF THE ABSORPTION AND BUILDUP FACTOR IN WATER FOR RADIUM, COBALT 60, AND CESIUM 137 GAMMA RAYS*

By K. I. PONNUNNI KARTHA,† GORDON N. KENNEY, and JOHN R. CAMERON MADISON, WISCONSIN

THE exposure rate, D_a , in air at any distance from a point source of gamma rays depends almost entirely on the inverse square law. At a point P, d cm. from a point source of S mc, it is given by:

$$D_a = \Gamma S/d^2 \qquad r/hr., \tag{1}$$

where Γ is the specific gamma ray constant in units of r cm.²/mc hr. In a water phantom the exposure rate at P is affected by two additional factors: (1) the absorption of the gamma rays in the water between the source and the point P, and (2) the buildup due to scattered radiation. The absorption factor, A, decreases the exposure rate while the buildup factor, B, increases it. The exposure rate D_v in water is related to the exposure rate D_a in air by:

$$D_w = A \cdot B \cdot D_a$$
 or $D_w/D_a = AB$. (2)

The commonly used tables of radiation distributions around linear radium sources have been prepared neglecting these factors, assuming that buildup effectively compensates for absorption. A. 6, 9, 15 A recent paper by Batho and Young, 1 however, does consider the tissue absorption near linear radium sources.

Experimental values of AB were determined using lithium fluoride thermoluminescent dosimetry. A photograph of the experimental arrangement is shown in Figure 1. Dosimeter capsules were supported on vertical plastic rods which were mounted on a plastic base. These capsules consisting of polyethylene tubing 1.5 mm. diameter×2 cm. length filled with LiF

powder, were placed at various angles from the source so that they would contribute minimum scatter to each other. These capsules were set vertically into the recesses drilled into the upper ends of the plastic holders. The dosimeters were placed at distances of 2, 4, 6, ... 14 cm. from the source. For each source two irradiations were performed: one in air with plastic around the LiF to produce electronic equilibrium, and the other in a water phantom 32 cm. \times 29 cm. \times 16 cm. in depth. The activities of the sources were 41.9 mg. radium (with 0.5 mm. Pt filtration), 43 mc cobalt 60 and 1∞ mc cesium 137. The dosimeters were left in their positions for various lengths of time so that the minimum exposure was greater than 40 r. After irradiation the dosimeters were read on a commercial reader.* At least three readings were obtained from each capsule; these had an average standard deviation of 1.6 per cent. The exposure rates as measured in air fit the inverse square law relation within experimental error $(\pm 2 \text{ per cent})$. The averages of these determinations of AB are listed in Table 1 and shown graphically in Figure 2. Experimental results obtained by other investigators12,13,14 are given in Tables II and III for comparison.

The theoretic value of A for monoenergetic gamma rays can be calculated from the equation:

$$A = {}_{\bullet} - \mu d. \tag{3}$$

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Table I

EXPERIMENTAL VALUES OF AB (ABSORPTION-BUILDUP) FOR RADIUM, COBALT 60,

AND CESIUM 137

Distance from the source in cm.	Radium	Cobalt 60	Cesium 137
2	0.98	0.98	0.95
4	0.95	0.95	0.93
6	0.90	0.89	0.90
8	0.88	0.86	0.84
IO	0.84	0.85	0.81
I 2	0.79	0.81	0.77
I 4	0.74	0.77	0.72

Table II

A Comparison of experimental values of ABFACTOR FOR RADIUM OBTAINED BY

VARIOUS INVESTIGATORS

Distance from the source in cm.	Authors	Ter- Pogossian et al. ^{12*}	Wootton et al.14*	Van Dilla and Hine ^{13*}
2	0.98	0.96	0.97	
4	0.95	0.94	0.94	0.98
4 6	0.90	0.92	0.88	0.94
8	0.88	0.89	0.82	0.90
IO	0.84	0.85	0.77	0.87
I 2	0.79	0.80		0.82
14	0.74	0.76		0.77

^{*} These values were obtained from the curves published by them.

Table III

A comparison of experimental values of ABFactor for cobalt 60 obtained by various investigators

Distance from the source in cm.	Authors	Wootton et al.14*	Van Dilla and Hine ¹³ *
2	0.98	0.98	
4	0.95	0.93	0.97
6	0.89	0.87	0.93
8	0.86	0.82	0.90
10	0.85	0.78	0.86
I 2	0.81		0.82
I 4	0.77		0.77

^{*} These values were obtained from the curves published by them.

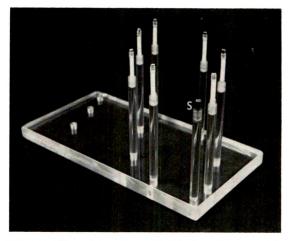


Fig. 1. Experimental arrangement showing the lithium fluoride dosimeters and the radiation source (S).

In this equation μ is the linear absorption coefficient in water for the particular energy of the gamma ray, and d is the distance from the source to the point being considered. If more than one gamma ray energy is present, the effective value of μ will change with distance from the source due to preferential attenuation of the lower energy components.

The buildup factor B is defined as the ratio of total dose from scattered plus unscattered photons to the dose from unscattered photons only. If D_s is the dose rate due to scattered photons and D_p the dose rate due to unscattered photons then:

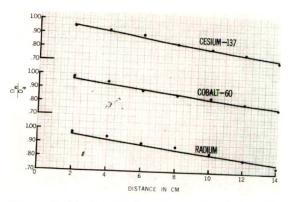


Fig. 2. D_w/D_a (or AB factor) as a function of distance. The lines represent the calculated values using equation (6) and the dots the experimental values.

$$B = I + \frac{D_{\bullet}}{D_{\bullet}}$$
 (4)

The value of B for a point source in an infinite medium has been studied by Goldstein and Wilkins⁵ for energies above 0.255 mev. and for $\mu d=1$, 2, 4, 7, 10, 15, and 20. An empiric relationship fitting these theoretic values for $\mu d=1$ and energies up to 2.0 mev. was developed by Hale.⁷ The constants of Hale's equation were re-evaluated for our cobalt 60 and cesium 137 experimental data to obtain:

$$B = \exp\left[\frac{0.73\mu d}{E^{0.06}}\right]. \tag{5}$$

Equations (3) and (5) are combined to obtain an expression for the AB factor:

$$AB = \exp \left\{ \left[(0.73/E^{0.06}) - 1 \right] \mu d \right\}, \quad (6)$$

which fits these data to within 2.4 per cent. The equation also fits the radium data within 3.2 per cent if the contribution of each gamma ray is considered individually (Fig. 2), or if the radium spectrum is approximated by two gamma ray energies of 0.55 and 1.65 mev. These calculations also take into account the different number of photons per r for each energy. When the radium spectrum is considered to be equivalent to an average energy of 0.8 mev., The agreement between the calculated and experimental results is within 3.6 per cent.

Although the experimental measurements do not include points in the important region between 0 and 2 cm., an extrapolation of the experimental curves indicates that the AB factors in this region are essentially unity for these sources.

CONCLUSION

Lithium fluoride thermoluminescent dosimeters were utilized to determine the combined absorption and buildup factors for three clinically important radioisotopes. The study discloses significant departures from the results predicted by the inverse square law when these radioisotopes are used in a water medium. For these sources

the buildup is insufficient to compensate for absorption. An empirical equation was evaluated for *AB* which fits the experimental data to within 3.2 per cent.

If absorption and buildup are neglected in dosimetry calculations for interstitial or intracavitary uses, over-estimation of the dose occurs. For example, in an intrauterine application, the magnitude of this error at anatomic points A, B, and at the pelvic wall is approximately 2 per cent, 8 per cent, and 12 per cent, respectively. These errors may be reduced by using the experimentally determined AB factors listed in Table 1 or calculated values using equation (6).

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DESIGN OF A UNIVERSAL WEDGE FILTER SYSTEM FOR A COBALT 60 UNIT*

By BERNARD S. ARON, M.D., D.M.R.T., and MICHAEL SCAPICCHIO, B.S. BROOKLYN, NEW YORK

WEDGE filters have been used in radiation therapy for the past 20 years. Their design and use with orthovoltage roentgen-ray therapy units, 1-4.8 linear accelerator 7.9 and the betatron 10 have been described by many authors. Cohen et al. 1-6 have described a wedge filter design in detail for use with a cobalt 60 teletherapy unit. In the present paper, the design, construction, and dosimetry of a universal wedge filter system, incorporating 4 wedge angles (15°, 30°, 45° and 60°), for use with a A.E.C. Ltd. Theratron F cobalt 60 rotational unit are discussed.

The purpose of constructing a wedge filter is to attenuate the primary beam of radiation differentially across one axis of a field (Fig. 1) in such a way that the isodose lines formed in this beam cross section assume an angle to the central axis of the beam. This angle is called the wedge angle and serves to designate a particular wedge filter. Calculation of wedge filters is possible with megavoltage radiation because of forward scatter. The percentage depth dose at a particular point in tissue depends on the primary component and the scatter component. As the scatter is predominantly forward rather than lateral, it can be directly related to the primary component, which can easily be calculated. Also, differential hardening by the thick edge of the wedge filter is negligible for megavoltage radiation. All that is required for calculating both wedge filters and wedge isodose curves is a normal (non-wedge) isodose curve and a half value layer curve for the wedge material used for cobalt 60 gamma ravs.

CONSTRUCTION OF WEDGE FILTERS

The Theratron F unit is designed for

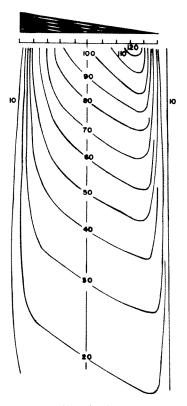


Fig. 1. 45° wedge filter isodose curve, 10 cm. field width.

use at 75 cm. source skin distance. The front plate of the collimator contains 2 cone slots; the one closest to the source is 38.5 cm. from the source (Fig. 2). The wedge filters are mounted on a lucite base plate which can easily be placed in this position. This transparent lucite plate allows proper alignment of the central axis of the wedge filter with the light localizer (Fig. 3). Lead was chosen as the wedge material because the half value layer for cobalt 60 gamma rays allows use of a wedge which is reasonably compact in size.

As the wedge filters are mounted at a distance from the cobalt 60 source, which

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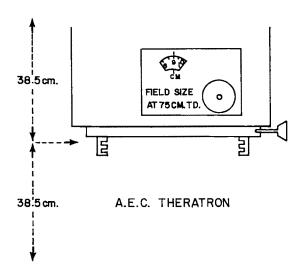


Fig. 2. Front plate of collimator with 2 cone slots and knob for setting field size on light localizer.

is one-half the source skin distance, the size of the filter (length and width) is onehalf the size of the desired field. The largest desired wedge field is 20 cm. \times 20 cm. and thus the largest wedge constructed is a 10×10 cm. wedge filter. This wedge filter may also be used for any smaller field size as long as the orientation of the central axis of the different field sizes coincides with the wedge central axis (Fig. 4). Actually, when a smaller field size is used (10 cm.), only the shaded portion of the wedge filter serves to differentially attenuate the beam of radiation. The remaining portion of the wedge filter contains the same thickness of lead across the beam and produces no differential attenuation; however, it does reduce the output. This is not a practical consideration as the maximum reduction of output is only about 40 per cent with the thickest wedge. This concept was verified by direct determination of isodose curves in a phantom, using multiple Sievert thimble ionization chambers for a small field (half the width of the wedge) and for a small wedge, which was constructed to be the same size and shape as the shaded portion of the wedge filter. The slopes of the 2 measured isodose curves were the same, within the limits of laboratory measurements. Thus, it is seen that a single wedge filter may be used as a univer-

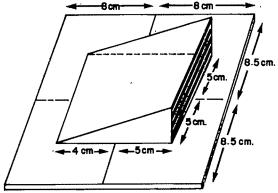


Fig. 3. Lead wedge filter mounted on lucite base plate. Base plate is scored along the central axis of the wedge filter.

sal filter, *i.e.*, it may be used for all field sizes. The field size itself is the collimator in the same fashion as for non-wedge fields.

CALCULATION OF WEDGE FILTERS

The method of calculating the thickness of individual wedge filters follows the method outlined by Tranter. The basis of this method is to determine the ratio of percentage depth doses of a wedge field isodose curve and a non-wedge field isodose curve for various points on both sides of the central axis. The appropriate thick-

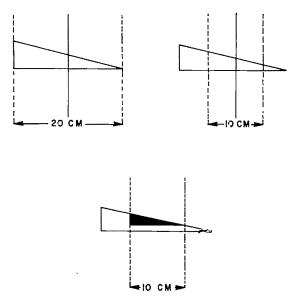
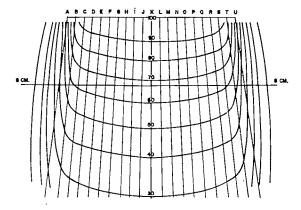


Fig. 4. Comparison of large (20 cm.) and small (10 cm.) field size for same wedge filter.

nesses of wedge filter material (lead) are determined from this ratio and the half value layer for lead for cobalt 60 gamma rays.

An example of the calculation of a 45° wedge filter is as follows:

- I. A depth is chosen for which the wedge filter is to be calculated. Since these wedge filters are primarily useful in the treatment of tumors of the head and neck region, a convenient depth is 8 cm. A line is drawn across the non-wedge isodose field at right angles to the central axis at this depth. Radian lines are constructed from the cobalt source which pass through the base of the non-wedge isodose curve spaced at I cm. from each other on both sides of the central axis. These radians will intersect the line at 8 cm. depth at 1.1 cm. from each other (distance= $75+8/75\times1.0=1.1$ cm.). The radians are then labelled alphabetically (Fig. 5).
- 2. A series of lines is constructed, parallel to one another, representing the new 45° to the central axis of the non-wedge isodose curve, intersecting this central axis at the same points of intersection as the non-wedge isodose lines (Fig. 6).
- 3. A chart is then made which includes the percentage depth doses at the points of intersection of the radian lines and the 8 cm. depth line for the non-wedge isodose curve and the 45° isodose lines (Fig. 7).



F10. 5. Radians and 8 cm. depth line constructed on a non-wedge 20 cm. isodose curve.

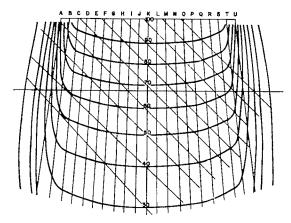


Fig. 6. New 45° lines constructed parallel to one another, intersecting central axis at same points of intersection as non-wedge isodose lines.

- 4. A ratio of the 2 percentage depth doses is made for each point. This ratio will be unity on the central axis, greater than unity on one side and less than unity on the other side. Each ratio is then expressed as a fraction of the largest one to determine the transmission ratio.
- 5. The primary radiation intensity along each radian must be reduced by this transmission ratio. The thicknesses of lead necessary may be obtained from half value layer curves for lead for cobalt 60 gamma rays. As the wedge filter is only one-half the width of the wedge field (see above), the physical design of the wedge filter can be accurately drawn, realizing that each radian is 0.5 cm. from the others rather than 1.0 cm. (Fig. 8).

This method of calculation may be used for any angle of wedge filter desired, the angle being chosen in Step 2 above.

	A	8	C	E	Œ	1	ĸ	M	0	Q	S	T	U
HON-WEDGE 19000SE	40	55	62	65	87	68	68	68	67	65	62	65	40
WEDGE ISODOSE	35	39	41	47	53	60	68	76	86	95	105	110	115
RATIO WEDGE	.875	.710	.600	.720	.790	.880	100	112	F58	L48	170	120	2 88
TRANSMISSION RATIO			.387	A25	.462	.515	.09	.68	.75	.04	1.0		
MM. PB.			15.2	13.6	12.2	10.5	8.3	6.5	4.5	2.3	0		

Fig. 7. Chart showing derivation of transmission ratio and thicknesses of lead. Values A, B, T, U, are neglected because they lie in penumbra region.

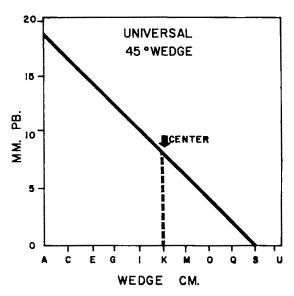


Fig. 8. Physical design of universal 45° wedge filter.

CALCULATION OF WEDGE ISODOSE CURVES

After the universal wedge filter (or filters) has been calculated and constructed, the isodose curves for any desired wedge field size may be determined using plain (non-wedge) isodose curves as a basis for calculation.

This method is, in essence, the reverse of the method of calculation of wedge filters outlined above. An example of the calculation of a 45° wedge isodose curve for a 20×20 cm. field size is as follows:

- 1. Radians are constructed on a non-wedge isodose curve of desired field size as described in Step 1 above (Fig. 9).
- 2. Using the transmission ratios for each radian as determined in Step 4 above, the percentage depth dose from the non-wedge field is multiplied by the appropriate transmission ratio for enough points so that the wedge isodose curve can be drawn (Fig. 10).
- 3. This "unnormalized" wedge isodose curve may be used in treatment planning in a similar fashion to non-wedge isodose curves. The dose delivered at a point in tissue is the percentage depth dose determined from this isodose curve multiplied by the output (r/min.) of the cobalt 60 unit.

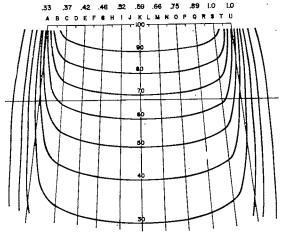


Fig. 9. Radians constructed on non-wedge 20 cm. isodose curve. The transmission ratio is noted above each radian.

4. However, it is customary¹-¹⁰ to use wedge isodose curves which have the same central axis percentage depth dose as non-wedge isodose curves. The "unnormalized" wedge isodose curve may be "normalized" (Fig. 11) by multiplying all the percentage depth dose values by the ratio of the percentage depth dose at the 1∞ per cent point on the central axis of the non-wedge isodose curve (1∞/59). When this "normalized" isodose curve is used, the dose

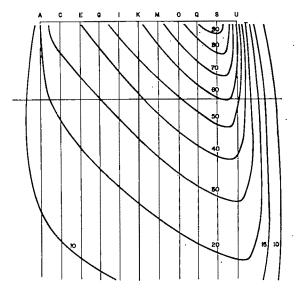


Fig. 10. "Unnormalized" 45° 20 cm. wedge isodose curve.

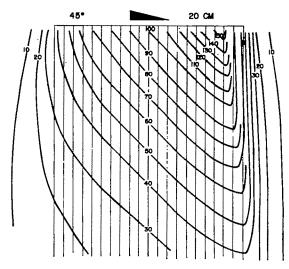


Fig. 11. "Normalized" 45° 20 cm. wedge isodose curve.

delivered at a point in tissue is the percentage depth dose multiplied by the "wedge output" for this particular wedge. The "wedge output" is the non-wedge output (r/min.) multiplied by the inverse of the ratio described above (59/100)—the "wedge factor."

Film dosimetry, using Ansco diagnostic film and a photometric densitometer unit, was used to check the wedge angles for the wedges constructed. There was satisfactory agreement between the calculated and measured wedge isodose curves.

Comparison of the wedge isodose curves obtained by the method outlined above and those obtained by Cohen et al.5 shows that the curves are similar. The wedge angle for individual isodose curves changes slightly with depth, being 45° at about 8-10 cm., slightly greater (50°) at shallow depths (5 cm.) and slightly less (40°) at greater depths (15 cm.). There is a hot spot which varies with field size (120 per cent for 10×10 cm. and 150 per cent for 20×20 cm.) for each wedge angle and increases with steepness of the wedge angle. The "wedge factors" (which decrease the output) are 84 per cent, 76 per cent, 59 per cent and 43 per cent for wedge angles of 15°, 30°, 45°, and 60°, respectively.

SUMMARY

The method used to design and construct a universal wedge filter system for a cobalt 60 unit is described. The system is universal in that all field sizes may be used with a single wedge filter for a particular wedge angle. These wedge filters and their isodose curves may easily be calculated and constructed.

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EVALUATION OF TOLERANCE DURING TREATMENT, LATE TOLERANCE, AND BETTER EVALUATION OF CLINICAL EFFECTIVENESS OF THE COBALT 60 MOVING STRIP TECHNIQUE*

By LUIS DELCLOS, M.D., and MARGARET MURPHY, B.S. HOUSTON, TEXAS

IT IS well known that when large volumes of abdomen have to be irradiated, it is no longer the local tolerance of the skin or subcutaneous tissue which limits the dosage but the tolerance of the abdominal organs and the general tolerance of the patient. Intolerance manifests itself by nausea, vomiting, diarrhea, and by a drop in the number of white blood cells and platelets in the circulating blood.

In a previous paper, the details of technique and a brief study of the tolerance were reported for the so-called "moving strip" technique. The purpose of this paper is to evaluate the tolerance of irradiation by this technique and to present up-to-date tables showing results in the original group of patients with ovarian carcinoma, lymphomas, and seminomas involving the abdominal cavity. These patients now have been followed 3 to 6 years, so that one can begin to evaluate the permanency of regional controls. The appearance of late complications must be carefully evaluated.

Irradiation of the abdomen *in toto*, using large fields, either parallel opposing or as a four-field arrangement, will limit the dose that can be administered to about 3,000 rads in 6 weeks at the expense of severe systemic reactions. It is likely that this dose will not be lethal to a high fraction of tumors

Based on the Manchester "moving strip" technique,² The University of Texas M. D. Anderson Hospital and Tumor Institute designed a similar technique to be used with a cobalt 60 unit which may be adapted

to any megavoltage unit by proper correction of depth dose and penumbra effect, provided that the beam is wide enough to cover the abdomen from side to side. A tumor dose of 2,800 rads can be delivered to each segment of the abdomen in 12 days, therefore being more effective biologically. This dose, if tolerated, should be lethal to a greater proportion of malignant growths.

The technique has been fully described previously. In summary, the abdomen is divided into a series of contiguous segments (Fig. 1, A and B), with the irradiation field moved slowly from one end of the volume to the other (moving strip).

STUDY OF TOLERANCE

From July, 1961 to January, 1963, a total of 49 patients with carcinoma of the ovary was treated with the "strip" technique and the tolerance was studied throughout the entire treatment.

All patients received a tumor dose of 2,800 rads. The treatment to the whole abdominal cavity was completed in 6 weeks.

The kidneys were shielded from the back with 2 half value layers of lead for cobalt 60, reducing the dose to the kidneys to 50 per cent of the tumor dose.

TOLERANCE DURING TREATMENT

Weight, hemoglobin/hematocrit, leukocytes, platelets, diarrhea, and nausea were recorded on the form shown in Figure 2. Average values for the 49 patients have been tabulated and graphed.

^{*} Presented at the Forty-sixth Annual Meeting of the American Radium Society, White Sulphur Springs, West Virginia, April 13-16, 1964.

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Fig. 1. (A and B) Photographs of patient showing skin marks during the treatment of the whole abdomen by the cobalt 60 moving strip. Lines are 2.5 cm, apart. Note kidney localization and shielding from the posterior field by lead placed in the "satellite platform," obtaining 50 per cent reduction of the dose to the kidneys. (Reproduced by permission of Radiology.')

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Weight. In spite of the high incidence of patients being affected by nausea and diarrhea at one time or another, the patient's weight is maintained, almost unchanged, throughout the whole treatment. This is due to the patient's diet, which is supervised by a dietitian who adjusts it to the patient's preferences and reactions during the treatment.

Hemoglobin and Hematocrit. Figure 3 (Graph 1) shows that hemoglobin and he-

PATIENT: MDAH #: AGE: 48 HISTOPATHOLOGY: Pa	pillary cys	t. adeno	SURGERY OPERATED OUTSIDE MDAH EXPLORATORY COMPLETE REMOVAL INCOMPLETE REMOVAL UNKNOWN OUTSIDE PALPABLE NOT PALPABLE UNKNOWN						RADIATION TREATMENT ABDOMEN PARALLEL OPPOSED FIELDS CO-60 MOVING STRIP PELVIS: BETATRON P.O.FIELDS OTHER		
PROGRESSIVE WEEKS	(START)	2	3	4	5	6	7	8	9	10	
GENERAL CONDITION	good	Good	Good	Gord	Good	Good					
WEIGHT	113.5	111.0	111.0	107	106	7.201					
NAUSEA	_	_	+	+	_	-					
VOMITING	_	_	-	+	_	_					
DIARRHEA	_	+	+	-	_	_					
WBC	8850	3450	3800	3950	3900	5220					
PLATELETS	382000	254000	280000	156000	224000						
HG/HT	12/35.5	11.6/38	12.4/39	124/39	11/33,	12.2/37					
SKIN (reaction).	~	-	1	_	_	_	_				
DYSURIA	_	-	1	-	_		-				
TUMOR RESPONSE	no tumo	- palp	able /	uot	forible						
MEDICATION	Confusine Poregric + Koopertate.	+ +	+	+	++	+	+				

B.U.N. 16 mg %

1.V.P.

KIDNEY SHIELD YEL

B. 120 / 2

BP 130/70 CHEST X-RAY YES CHEGATIVE). ASSOCIATED DISEASE ND.

* abdominal rear

Fig. 2. Recording chart used to evaluate the reactions of the patient during the treatment with the cobalt 60 moving strip technique.

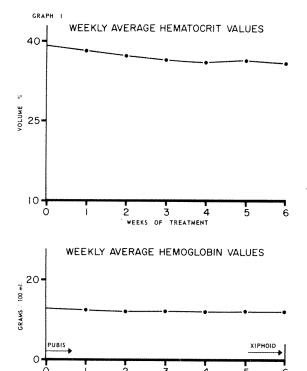


Fig. 3. Graph 1.

WEEKS OF

TREATMENT

matocrit values are not affected by the treatment.

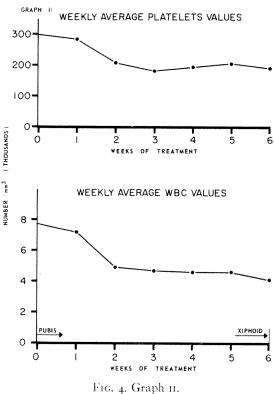
Leukocytes and Platelets. Leukocytes and platelets in the circulating blood will drop to about 60 per cent of the initial value during the first 2 weeks of treatment. After the second week, there is the general picture of a slow decrease in values (Fig. 4, Graph II). Both will return to normal values soon after completion of treatment.

Diarrhea. Diarrhea may also start at any time (Fig. 5, Graph III), the second week being the most common (lower abdomen irradiation); it tends to decline afterwards. The use of paregoric (4 cc.) after each bowel movement and a low residue diet will help to minimize the condition.

Nausea. At any one time during treatment (Fig. 5, Graph III), at least 24 per cent of the patients experienced nausea. More patients experienced nausea in the



Fig. 5. Graph III.



GRAPH III WEEKLY OCCURRENCE OF DIARRHEA TOTAL OCCURRENCE

100-

75

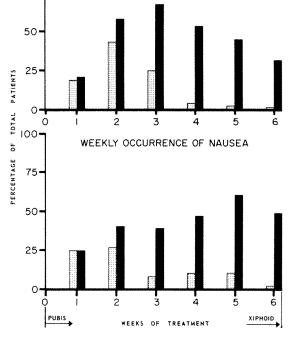


TABLE I

THREE YEARS MINIMUM EVAULATION OF 41 CASES OF OVARIAN CARCINOMA INVOLVING THE ABDOMINAL CAVITY TREATED BY COBALT 60 MOVING STRIP ALONE OR IN COMBINATION WITH OTHER TECHNIQUES*

November, 1957-January, 1961

		Addi	tional Tre	atment		Status (years between parentheses)					
Pathology Extension	None	None Pelvis† Radium Alive		Alive	Alive with Disease	Dead before					
	Tumor removed		I				1 (1.5)				
n:!!	Unknown extent	2	I		I (6) I (4)		1 (0.5)				
Papillary Cystadeno-	Spillage	3			I(6) I(6)		1 (0.5)				
carcinoma 31 Residual tumor in pelvis Residual tumor in abdomen	2	1	1			I (I) I (I.5) I (4.5) I (I.5)					
	tumor in	11	5	4	I (4.5) I (I.5) I (4.5)	1 (5.5)LS‡	I (0.5) 3 (I) 2 (I.5) 2 (2) I (2.5) I (0.5) I (2) I (2.5) 2 (I.5) I (2) I (2.5)				
Undiffer- entiated	Residual tumor in pelvis	1	I				1 (1)				
tumor	Residual tumor in abdomen	5	1	2			2 (0.5) 2 (1) 1 (1.5) 1 (2) 1 (0.5) 1 (1)				
	Total				7	I	33				

* Doses between 2,000 and 3,000 r.

† Two parallel opposing fields, 22 mev. betatron, tumor dose 2,000 rads/2 weeks.

5 Tandem and ovoids (uterus left in).

‡ LS-patient on L-sarcolysin.

fifth week (upper abdomen irradiation) than in any other week. First experience of nausea occurs most frequently in the first 2 weeks. Nausea can be minimized by the use of compazine, 10 mg. 3 or 4 times daily, half an hour before meals; the same drug given by intramuscular injection before the daily irradiation has been found very helpful in patients resistant to the oral drug.

The pattern of nausea experience is consistent for each group of patients classified according to first occurrence of nausea; it tends to remain present after first occurring, but to a lesser degree.

LATE COMPLICATIONS

No clinical manifestations of kidney or spinal cord damage have been observed. Since these complications occur within the first 2 years after completion of treatment, and a minimum period of 3 years has now elapsed in the study of the original group of patients, we can claim that the technique is safe.

STUDY OF EFFECTIVENESS

Since the length of follow-up is still limited, only a preliminary evaluation of the original patients with tumors of the ovary (Table 1), testis (Table 11), and lymphomas involving the abdominal cavity (Table 111) is presented. These tables have been presented previously, but the cases have been reviewed and brought up to date.

Forty-one patients with ovarian carcinoma were treated between December, 1957 and January, 1961 with the cobalt 60 moving strip technique (Table 1). Additional treatment at the completion of the abdominal irradiation was given to the pelvis when pelvic masses were felt; the dose

79

TABLE II

evaluation of 7 cases of testicular tumors with extensive lymph node enlargement involving the abdominal cavity treated by cobalt 60 moving strip alone or in combination with other techniques*

November, 1957–January, 1961

Extension Pathology outside Testis			Additional Treatment (after strip)	Sta	Complications	
	1	Right inguinal	Right inguinal (3,000 r in 3 weeks)	NED	3 LF	_
	I	Pampiniform plexus	Mediastinum (1,500 r); left supraclavicular (2,000 r); right inguinal (3,000 r)	NED	6	_
Seminoma 5	I	Abdominal mass	Residual mass (1,000 r); right inguinal (3,750 r); mediastinum (2,500 r); left supraclavicular (3,000 r)	NED	4	
	I	Abdominal mass	Mediastinum (1,560 r); scrotum (1,200 r); left supraclavicular (3,000 r)	NED	5 · 5	_
	I	Abdominal mass	Residual mass (2,000 r); mediastinum (2,500 r); left supraclavicular (2,500 r)	NED	3.5	_
Embryonal	1	Spermatic cord	Right inguinal (4,000 r)	NED	1.5	Expired in car crash at 1.8
Carcinoma 2	1	Abdominal mass			ized disease er treatment)	years

^{*} Doses between 2,000 and 3,000 r with doses other than strip given at a weekly rate between 1,000 and 1,500 r. NED=no evidence of disease.

was 2,000 rads in 2 weeks from a 22 mev. betatron unit delivered through parallel opposing portals. Alternately, if the uterus had been left in place, a radium insertion with tandems and ovoids was performed. (These patients now have from 4 to 6 years follow-up, so that one can begin to evaluate the permanency of regional controls.)

Seven patients are alive for 4 years (3 for more than 6 years). One patient is alive after 5 years with clinical evidence of disease, and 33 patients expired at different intervals up to 2.5 years after starting their treatment, except for 1 patient who expired at 4.5 years.

Table II shows the results in 7 cases of malignant testicular tumors. It will be noted in the seminoma group that despite the presence of large abdominal masses in 3 patients, all of them are alive after 3.5 years, 2 patients for more than 5 years and I for more than 6 years.

Table III shows the results in 17 cases of malignant lymphoma treated between December, 1957 and January, 1961 by the cobalt 60 moving strip technique. Seven

are alive for more than 3.5 years, 3 for more than 5 years and I for more than 7 years, in spite of the advanced stage of their disease.

SUMMARY

Irradiation of the entire abdomen is the logical therapy for ovarian carcinomas spread throughout the abdominal cavity, seminomas with massive periaortic lymph node involvement, and abdominal manifestations of the lymphomas. When irradiation is done either with kilovoltage or megavoltage, through large portals, marked systemic reactions can only be avoided by long protraction; it is likely that the dose administered will not be lethal to a high fraction of tumors.

A moving strip technique using megavoltage is better tolerated. In this paper it is shown that a dose of 2,800 rads can be delivered to each segment of the abdomen in 12 days with local systemic reactions kept within safe limits during the treatment.

A minimum period of 3 years has now

E = expired.

LF = lost to follow-up.

TABLE III

EVALUATION OF 17 CASES OF MALIGNANT LYMPHOMA INVOLVING THE ABDOMINAL CAVITY TREATED BY COBALT 60 MOVING STRIP ALONE OR IN COMBINATION WITH OTHER TECHNIQUES*

November, 1957-January, 1961

			D	egree of	Extension			Status (yr.)			
Pathology	LN's	GI	Liver	LN's+ GI	LN's+ Spleen	LN's+ Liver+ Spleen	LN's+ GI+ Liver	Alive at	Dead at	Cause of Death	
Hodgkin's Granuloma 8	1 1 1	1		ī		1	1	3 · 5	4 · 5 1 · 5 4 · 5 1 1 · 5 4 · 5	G+Septicemia G+AR G G+AR	
Lymphosarcoma 4	I	1		I				5 7 3.5 LF 3.5		_	
Reticulum Cell Sarcoma 3	2	h of the second second second second				i		V III HAAMA	1 (3) 1 (6.5) 1	G G ?	
Giant Follicular Lymphoma 1			The second secon		I			4			
Lymphoma 1			I						I	Liver recurrence (treated to 1,500 r	
Total 17								7	I O		

^{*} Doses between 2,000 and 3,000 r. LN's= retroperitoneal lymph nodes, GI=gastrointestinal tract.

AR = abdominal recurrence. G = generalized.

?= unknown. LF= lost to follow-up.

elapsed in the study of the original patients, which makes an assessment of the late complications possible. No kidney or spinal cord sequelae have been observed.

The original patients now have a minimum of 3 years follow-up, so that one can begin to evaluate the permanency of local controls.

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The authors are indebted to Lillian M. Fuller, M.D., Associate Radiotherapist, for her contribution on malignant lymphomas.

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RESULTS OF COBALT 60 ROTATION THERAPY IN CARCINOMA OF THE CERVIX*

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IN THE treatment of carcinoma of the cervix uteri, radiation therapy is one of the more satisfying procedures. Increased survival rates compensate for the effort expended. A more thorough understanding of the nature of this disease, its radiobiology, ¹⁷ the sites and rates of spread through the cervical lymphatics, ⁹ its clinical course and its radiocurability, ⁶ has resulted in a steady increase^{2,19} in the survival rate. The advent of supervoltage radiation made available a more effective therapeutic agent for treating deep-seated tumors.

In this paper a method of treating carcinoma of the cervix by a rotation technique with a cobalt 60 teletherapy machine is described and the results are given. It is simple and reproducible, and the results, in our opinion, are better than those with older methods.

The method consists of treating the cervix, the adnexa and possible lymph node metastases in the confines of the pelvis to a dose of 4,000 r by rotation, then decreasing the field to include only the cervix and known residual disease to an additional dose of 3,000 r.

A somewhat similar method was first used by Trump *et al.*²³ and by Mellor.¹⁶ A preliminary report on this method was given by us in a previous publication.¹⁵

METHOD

The projection of the volume to be treated is marked anteriorly on the patient, and the lateral projection of the central axis of the lesion is marked on the side of the patient. This region extends from one lateral pelvic wall to the other transversely, and from the sacral promontory to a point overlying the ischial tuberosities along the

long axis of the body. This cross section measures approximately 15 cm. ×15 cm., but varies according to the size of the individual. The volume treated should include the lymph nodes draining the cervix. The shape of the volume treated is a cylinder, with the diameter equal to the transverse dimension, and the length equal to the dimension along the long axis of the patient.

The patient is placed supine on the treatment table. The diaphragm on the cobalt 60 machine is adjusted to give the field size, as outlined on the skin, at the center of rotation. The center of the field anteriorly is marked by a cross. The machine is then turned 90° and the patient is raised or lowered until the center of the field matches the previously drawn line on the side of the patient (Fig. 1). The patient is fixed in this position and the machine is turned back to 0°. Now, by adjusting the light distance gauge, the source skin distance can be



Fig. 1. Patient outlined for therapy and setup on the lateral skin mark.

^{*} Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8–10, 1965. From the Radiation Therapy Department of Presbyterian Unit Hospital of the United Hospitals of Newark, New Jersey.

found and recorded. For subsequent setups this source skin distance is used. The set-up then consists of setting the diaphragm openings and the source skin distance, and positioning the patient so the center of the field is at the anteriorly marked cross at the given source skin distance. The center of the lesion is always at the axis of rotation.

In order to make certain that the region to be treated is centered correctly, "verification films" are taken, using the gamma radiation from the cobalt machine. A small vaginal cone is inserted into the vagina against the cervix. The patient is set up as for treatment with the same size of field. With Kodak Blue Brand film in a cardboard cassette with the leaded side facing the radiation, the exposure for the treated field is 4/3 r. The field is then opened wide and the film kept in exactly the same position as for the treated field. The exposure for this field is 2/3 r. We make a posteroanterior exposure and a lateral exposure (Fig. 2 and 3).

The total tumor dose for the large volume has been about 5,000 r but more recently about 4,000 r. This is given in daily tumor doses of 200 r, but may be less, according to how the treatments are toler-

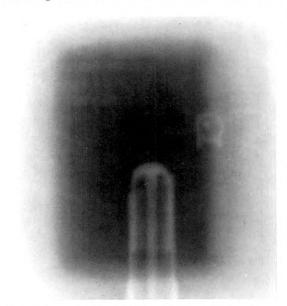


Fig. 2. Posteroanterior verification film of small field.

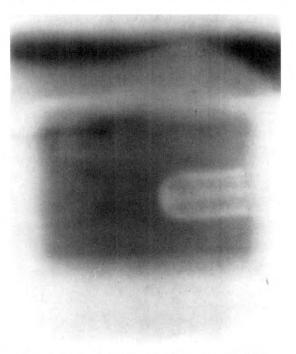


Fig. 3. Lateral verification film of small field.

ated. The time in minutes to deliver the given tumor dose is easily found by the use of our Rotation Therapy Time Chart, where average thickness of the patient is charted versus the time in minutes to give 100 r tumor dose for the different sizes of fields (Table I). The average thickness in centimeters is the average of the patient's anteroposterior measurement and the lateral measurement, both taken through the center of the lesion. The difference between the time calculated by this method and the time calculated by using twelve 30° sectors is generally less than 4 per cent.

At the end of 4 or 5 weeks, the patient is examined to determine the extent of residual disease. The field is then decreased in size so that the cervix and the residual disease are in the irradiated field. This field size may vary from 5 × 5 cm. to 12 × 13 cm. The tumor dose to this irradiated volume is 3,000 r, 200 r per day for a period of 3 weeks.

ISODOSE CURVES

The isodose curves for a field 15×15 cm. are given in Figure 4 in per cent of tumor

TABLE I

C-1000-COBALT 60 UNIT ROTATION THERAPY TREATMENT TIME CHART

55 cm. s.a.d.

Time in minutes to give 100 r tumor dose for different thicknesses for period April 1, 1964 through June 30, 1964 Output 35.7 r/min. at 55 cm. S.A.D.

Average Thick-		Are	a in sq.	cm.	
ness in	50	100	150	200	400
cm.	min.	min.	min.	min.	min.
10 11 12 13 14	3.22 3.29 3.39 3.44 3.56 3.65	3.12 3.18 3.28 3.32 3.42 3.50	3.08 3.14 3.21 3.28 3.36 3.42	3.05 3.08 3.14 3.21 3.30 3.36	2.95 2.98 3.06 3.12 3.15 3.22
16 17 18 19	3.75 3.85 3.96 4.13 4.20	3.60 3.66 3.77 3.85 3.96	3.50 3.60 3.66 3.77 3.87	3·43 3·51 3·61 3·71 3·77	3.29 3.36 3.43 3.50 3.60
21 22 23 24 25	4.32 4.48 4.61 4.71 4.88	4.08 4.19 4.31 4.41 4.56	3.96 4.08 4.19 4.28 4.39	3.85 3.96 4.08 4.19 4.28	3.65 3.74 3.82 3.90 4.01
26 27 28 29 30	5.01 5.17 5.31 5.47 5.63	4.68 4.80 4.96 5.06 5.20	4·53 4·61 4·75 4·88 5·01	4·39 4·51 4·61 4·71 4·86	4.08 4.15 4.24 4.34 4.43

dose, and in r if 4,000 r is taken as the tumor dose.

The isodose curves for an 8×8 cm. field are shown in Figure 5 in per cent of tumor dose, and in r for a tumor dose of 3,000 r.

The isodose curves for the combined fields, 4,000 r for the larger and 3,000 r for the smaller volume, are shown in Figure 6.

The cervix and volume irradiated by the smaller field receives 7,000 r; the lymph node bearing parametrial region, approximately 5,500 r; the rectum, a dose between 5,600 r and 6,300 r; the bladder, a dose between 4,900 r and 6,300 r; the skin an-

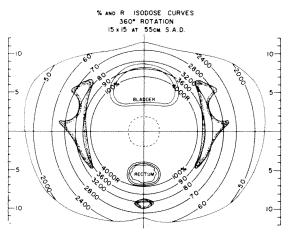


Fig. 4. Isodose curves for 15×15 cm. field in per cent of tumor dose and in r for a 4,000 r tumor dose.

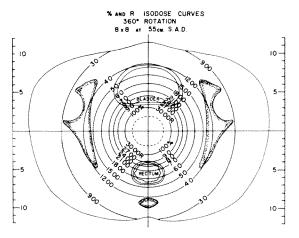


Fig. 5. Isodose curves for an 8×8 cm, field in per cent of tumor dose and in r for a tumor dose of $3,\infty$ 0 r.

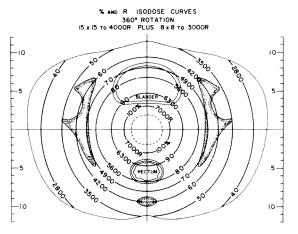


Fig. 6. Isodose curves for combined fields 15×15 cm. to 4,000 r and 8×8 cm. to 3,000 r.

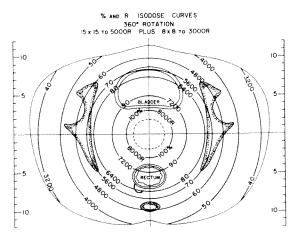


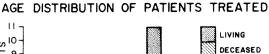
Fig. 7. Isodose curves for combined fields 15×15 cm. to 5,000 r and 8×8 cm. to 3,000 r.

teriorly and posteriorly, approximately 3,500 r; and the skin laterally, approximately 2,500 r. Of course, these dosages are approximations and vary with the size of the large field and the size of the smaller field.

The isodose curves for the combined fields, 5,000 r to the larger volume and 3,000 r to the smaller volume, are shown in Figure 7.

ANALYSIS OF PATIENT MATERIAL

This is a study of 55 cases available for evaluation. All patients with cancer of the cervix uteri and with no previous radiation therapy, or surgery within 2 years prior to radiation therapy, regardless of age, complications, diseases or stage of disease, are included. The earliest treatments were in



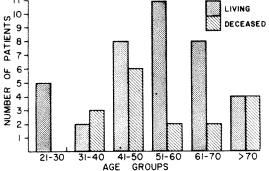


Fig. 8. Bar graph of age distribution of treated patients.

1957, and the analyses include all those who completed treatment by January, 1964. No patients were treated by this method during 1958 and 1959, for we did not know what the complications would be.

A positive pathologic diagnosis of carcinoma was obtained before any therapy was given. Fifty-two cases were identified as squamous cell carcinomas, and 3 as adenocarcinomas. In 10 patients cervical carcinoma was present in the cervical stump. These had had a supracervical hysterectomy 5 to 20 years prior to therapv.

The greatest incidence of disease occurred in the 41-60 year age groups. The youngest woman was 25 years old and the oldest 82 years old. In Figure 8 the age distribution is shown in a bar graph.

All patients were married. Ten had

TABLE II PAST PREGNANCIES IN CANCER OF THE CERVIX

		and the second s	Pregnant						
Marital Status	0	1	2	3	4	5	>5	No.	Per Cent
			F	or Living	g Patien	ts			
Married	4	6	6	9	1	2	10	34/38	90
** * AVAMA MARKET THE THE THE THE THE THE THE THE THE T			Fo	r Deceas	ed Patie	nts			
Married	6	T.	5	I	1	2	I	11/17	65

tation therapy did not of itself produce pelvic fibrous healing. Localized thickenings in some portions of the pelvis did occur, but only with advanced disease.

DISCUSSION

Rotation cobalt 60 therapy has been found to be an effective, simple, easily applied technique for treating cervical cancer in patients of all sizes. It is an "all external" treatment method, and uses no radium or supplemental modalities. Hospitalization and operating room procedures are not necessary. It can be duplicated in the average-sized hospital with a rotational cobalt 60 therapy machine. The irradiated volumes in the pelvis receive fairly homogeneous radiation without hot or cold areas. The use of dosage tables for rotational therapy, which give the time to deliver a tumor dose of 100 r for different thicknesses of patient, makes this technique easy to apply.

The isodose curves for 360° rotation are given in Figures 4 through 7. Whether such configurations are best suited for pelvic viscera is debatable. While it is true that a tumoricidal dose is delivered to the lateral pelvic walls, the rectum and the bladder also receive high doses of radiation. Since the rectum and the bladder lie very close to the uterus and the cervix, (0.5 to 3 cm.), and since the most frequent spread of cervical cancer is by direct extension,2.9 active carcinoma may exist close to these structures even though penetration through the walls of these cavities may occur late. The question is, therefore, whether one should reduce dosage at these sites to less than a possible curative dose (less than 5,000 r) in order to prevent rectal and bladder reactions.20,22 How can one deliver a sterilizing dose to points 2 to 5 cm. lateral from the cervix and then, at 2 to 3 cm. anteriorly and posteriorly, reduce the dose to 3,000-4,000 r? Theoretically, this can be done with radium, but the history of radium applications in actual practice has been fraught with many problems.21 Some of our radium difficulties were

as follows: Difficulty in duplication, inaccurate dosage calculation, hot and cold spots, varying vaginal vaults with stenosis and/or bulky cervical masses. Certain patients, because of poor general condition, were not able to withstand even a minor surgical procedure. Our all-external mode of therapy obviated all of these.

It may be possible to change the isodose curves, to reduce the bladder and rectal doses. Blockage over the bladder and the rectum by "skip" areas, where the beam is automatically shut off at preset angles, or rotation through less than 360°12 or rotation around two different centers of rotation, 16 one on each side of the pelvis, may produce desirably shaped isodose curves. However, before using any other than 360° rotation, one must know the isodose curves which are produced. Otherwise, one may over-irradiate the structures which one wants to spare and under-irradiate the disease areas. The important aspect of the method here presented is that it is simple, easy to duplicate, and effective in its results, without detractive morbidity.

The results, reactions and complications in this study are based mostly on a tumor dose of 5,000 r to the larger pelvic volume and 3,000 r to the cervix and to the residual disease in the smaller treated volume, given in a period of 8 weeks. With this dose the proximal walls of the rectum and bladder receive approximately 7,000 r. Toward the latter part of this work, the tumor dose delivered to the larger volume has been reduced to 4,000 r. This reduces the dose to the proximal walls of the bladder and rectum to about 6,000 r. The lymph node sites near the pelvic walls receive about 5,500 r. The large field is kept within the confines of the pelvic walls as indicated by "verification films", and the small volume is kept as small as possible, consistent with covering the cervix and residual disease. Our large port now is seldom larger than 15×15 cm. These changes have decreased the degree of diarrhea and dysuria. No case of persistent diarrhea or rectal bleeding has occurred since the change. The over-all

well-being of patients also appears improved.

In planning therapy to small, thin patients or old, diabetic or rheumatoid patients, it is advisable to be cognizant of their low tolerance to even average daily tumor doses of 200 r. Accordingly, greater protraction may be advisable.^{4,5,18}

Radical pelvic surgery, when it follows soon after the completion of radiation therapy, is not well tolerated. This procedure should be employed only when absolutely necessary. Resections of heavily irradiated pelvic structures have produced severe fibrosis in some of our cases and should be avoided when possible.

One should be aware that previous pelvic inflammatory disease or surgery may have produced fixed loops of small bowel near the uterus and a large dose to these structures can produce serious complications, and even perforation, in their walls.

Our results were obtained without noticeable morbidity. Although diarrhea is the principal symptom during treatment, it was a complication in only 3 patients, 5.4 per cent. High rectal dosage is unavoidable but has been compatible in this series with the fundamental aim of planning for the best survival with a minimum of acceptable reactions. Ingelman-Sundberg of the Radiumhemmet has demonstrated in a series of rectal reactions in cervical carcinoma that the 5 year cure rate in these patients was 12 per cent better than in those similarly treated without rectal changes. 7,10

SUMMARY

- 1. A method of treating carcinoma of the cervix with a cobalt 60 teletherapy machine, using 360° rotation, and irradiating a larger and then a smaller volume in the pelvis is described.
- 2. Isodose curves are given for the distribution of dose in a body cross section, in per cent of tumor dose and in r for the following conditions: when a tumor receives (a) 4,000 r, (b) 3,000 r with the smaller field, (c) a combination of these two, and (d) a combination of 5,000 r to the

larger field and 3,000 r to the smaller field.

- 3. An analysis is made of the patient material, 55 cases, giving the pathology of the tumor, the stages of the disease, the marital status, the number of pregnancies, the symptoms which brought the patient to the physician, and the age distribution.
- 4. The results of this method of therapy are given. The survival with no evidence of disease is 86 per cent in Stage I, 80 per cent in Stage II, 67 per cent in Stage III and none in Stage IV. The over-all survival is 67 per cent. The more advanced cases in Stage III show the greatest improvement in survival rates.

The survival rates are compared with those of other investigators using radium and external irradiation, and are found to be equal if not better.

- 5. Reactions due to therapy are described. The number of cases having diarrhea and dysuria are charted. These symptoms were generally mild and controllable.
- 6. The surgical procedures post therapy that were performed were examined and the findings are discussed.
- 7. Methods by which improvement in isodose distribution may be obtained are presented.

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CARCINOMA OF THE UTERINE CERVIX ASSOCIATED WITH PREGNANCY*

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CARCINOMA of the uterine cervix complicated by pregnancy has been and remains a subject of considerable discussion. The medical literature contains diverging opinions regarding reciprocal interrelationships between these two conditions; this is so particularly in the etiologic, therapeutic, and prognostic aspects. Some of these divergent opinions are listed in Table 1.

The incidence of carcinoma of the cervix among pregnant women shows variable rates in different reports, ranging from a minimum of 1 case in 10,000 pregnancies to a maximum of 13 cases in 10,000 pregnancies. 4,28,88,44,46 Reports from large maternity hospitals give an average incidence rate of

I cervical cancer case per every 2,500 gestations. 3,15,19,25,31,40,41 Publications from cancer centers reveal that around I per cent of women with carcinoma of the uterine cervix are pregnant at the time of diagnosis (Table 11). The observed variations in incidence of carcinoma of the cervix associated with pregnancy in different reports are related to the fact that some series include patients with the initial diagnosis being made up to the end of the first postpartum year, while others limit their series to cases discovered during pregnancy. Furthermore, some series also include carcarcinoma in situ cases. Waldrop and Palmer⁴⁰ consider it justifiable to include postpartum cases in series of patients with

Table I

RECIPROCAL EFFECT OF PREGNANCY AND CARCINOMA OF THE UTERINE CERVIX

Effects	Reference				
Carcinoma of the cervix prevents pregnancy Pregnancy prevents carcinoma of cervix	4, 20, 24 4 ¹				
2. Pregnancy accelerates tumor growth Pregnancy retards tumor growth	4, 9, 20, 23, 45 2, 6, 8, 36, 42				
3. Estrogens predipose to carcinoma of cervix Estrogens control carcinoma of cervix	1, 18, 28 46				
4. Youth has worse prognosis Youth has better prognosis	6, 8, 23 40, 42				
5. Vaginal delivery is a contraindication	3, 5, 7, 10, 14, 16, 17, 19, 20, 22, 23, 25, 26				
Vaginal delivery is not a contraindication	29, 31, 32, 41, 43, 44, 45 12, 30, 40				
6. Surgery is the primary treatment of choice Radiotherapy is the primary treatment of choice	6, 7, 23, 31, 39, 45 4, 5, 10, 11, 12, 16, 17, 20, 21, 22, 26, 27, 30, 34, 40, 43, 44				

^{*} Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8-10, 1965.

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	Table II	
FREQUENCY OF PREGNANT AND I	YEAR POSTPARTUM CASES IN WOMEN	WITH CERVICAL CARCINOMA

	Total No. of Cases	Pregnant	Post Partum	Total
Radiumhemmet ¹¹	7,192	82 (1.1%)	157 (2.1%)	239
Roswell Park Memorial Institute ⁴⁰	6,000	52 (0.9%)	132(2.2%)	184
M.D. Anderson Tumor Institute ²² I. González Martínez Oncologic	2,191	28 (1.3%)	83 (3.8%)	III
Hospital Puerto Rico	2,736	26 (1.0%)	40 (1.5%)	66

carcinoma of the cervix associated with pregnancy due to the following facts: (a) The carcinoma is usually diagnosed few months after delivery; (b) in this group, patients usually present symptoms during pregnancy or shortly after delivery; and (c) the stage of the disease in the postpartum group is more advanced than in those where the diagnosis has been made during pregnancy, indicating that the cancer had been present for a longer time.

Present diagnostic techniques favor the early diagnosis of cervical carcinoma. Inspection and palpation of the uterine cervix are definitely not adequate to rule out the diagnosis of carcinoma in a pregnant woman; smears of the cervix for exfoliative cytology examination should be taken routinely at the time of the first prenatal examination and in the postpartum period. Carcinoma of the uterine cervix should be considered in the differential diagnosis of all cases showing bleeding during pregnancy.

In this report, a review of the experience with this disease at the I. González Martínez Oncologic Hospital in San Juan is presented.

MATERIAL

In this study only the cases with invasive carcinoma of the cervix are included; all patients with carcinoma *in situ* were excluded. Of 2,736 cases of carcinoma of the cervix uteri treated at the I. González Martínez Oncologic Hospital during the period 1941 to 1964, sixty-six cases (2.4 per cent) were found related to pregnancy; this means that the disease was diagnosed

during pregnancy or within I year after its termination. Table II shows the relationship of these two groups. Table III shows the distribution of cases diagnosed in the different trimesters of pregnancy and in the postpartum period.

In Table IV the most common symptoms described by our patients are listed. The most frequent symptom, vaginal bleeding, occurred in 80 per cent of patients. Abdominal pain was the only symptom in 4 patients, and vaginal discharge was noted in 3. Of the entire group, only 6 had no symptoms, and in 5 of these the lesion was discovered on a routine prenatal examination. The average duration of symptoms was 3.7 months in the pregnant group and 5.5 months in the postpartum group.

Age and its relationship to prognosis in carcinoma of the uterine cervix have been

TABLE III

CASE MATERIAL, CARCINOMA OF THE CERVIX
ASSOCIATED WITH PREGNANCY AND
I YEAR POST PARTUM

	No. of Cases	
Pregnant		26
1st trimester	8	
2nd trimester	8	
3rd trimester	9	
Post Partum		40
1 to 3 months	14	
4 to 6 months	10	
7 to 9 months	9	
10 to 12 months	7	

TABLE IV
FREQUENCY OF MAIN SYMPTOMS

Symptom	No. of Cases
Vaginal Bleeding	53 (80%)
Abdominal Pain	4 (6%)
Leukorrhea	3 (5%)
No Presenting Symptoms	6 (9%)
Total	66

amply discussed in the medical literature. It has been stated that the prognosis in cervical cancer cases is worse in the younger age group, 6.8.20 but this was not confirmed by Waldrop and Palmer whose experience showed a more favorable prognosis in the younger age group which tended to have less advanced disease. Table v shows the age distribution of the cases in this series. The youngest patient was 22 years old and the oldest 48 with an average age of 35.5 years and a median age of 37 years.

Parity has been considered an important factor in the etiology of carcinoma of the cervix uteri; this neoplasm is known to occur more frequently in multiparous patients. Table VI shows the distribution of our patients by number of deliveries. The average number of deliveries was 7.4. Fifty seven of the total of 66 patients in our study had more than 4 pregnancies.

In Table VII the histopathologic diagnosis of the patients in this series is listed. Sixty patients (91 per cent) had the diagnosis of squamous cell carcinoma of the

Table V
AGE DISTRIBUTION

Age	No. of Cases	
20-24	ı (1%)	
20–24 25–29	10 (15%)	
30-34	13 (20%)	
35-39	27 (41%)	
40-44 45-49	13 (20%)	
45 49	2 (3%)	
Total	66	

TABLE VI

No. of Deliveries	Diagnosed During Pregnancy	Diagnosed Post Partum	Total
I	2	2	4
2-3	4	I	5
2-3 4-6	8	14	22
7-9	5	10	15
10-14	6	12	18
15+	I	I	2
		******	******
Total	26	40	66

cervix and only 2 showed adenocarcinoma. In 4 patients the diagnosis of anaplastic carcinoma was rendered.

STAGE OF THE DISEASE

Carcinoma of the cervix associated with pregnancy is usually diagnosed in the early stages of the neoplastic disease. 11,14,87,40 Table VIII shows the distribution of the cases in our series, correlating the time when they were discovered and the stage of the disease. Noteworthy is the fact that the patients with the disease diagnosed during pregnancy had a predominance of Stage I lesions and none were found more advanced than Stage II. However, patients diagnosed in the postpartum period showed that the disease had extended outside the cervix in the majority of cases with a significant number in the Stage III and IV categories.

TREATMENT

There is no unanimity of opinion regarding the treatment of choice of carcinoma of the cervix associated with pregnancy; some authors advocate surgery, 23,81,89 while the majority prefer radiotherapy as the primary treatment. 10,11,12,21,22,26,40,43

There may be differences of opinion as to which treatment modality is best, but there is agreement as to when to begin treatment. During the first and second trimesters, the case should be treated without delay and no consideration to save the

Table VII

HISTOPATHOLOGIC DIAGNOSIS IN A GROUP OF CASES OF
CARCINOMA OF THE CERVIX ASSOCIATED

WITH PREGNANCY

Histologic Type	No. of Cases	
Epidermoid	60 (91%)	
Anaplastic	3(4%)	
Adenocarcinoma	2 (3%)	
Not Classified	1 (2%)	
	North-Colon	
Total	66	

fetus should be made. In the third trimester, the baby should be delivered by cesarean section as soon as viable, and then primary treatment should be instituted.

The primary treatment for carcinoma of the cervix associated with pregnancy at the I. González Martínez Oncologic Hospital is irradiation. The usual treatment for patients during the first and second trimesters is external irradiation followed by intracavitary radium application. In the third trimester, after the fetus is viable, a classic cesarean section is done. As soon as the patient has recovered from the operation, external irradiation and intracavitary radium application are carried out.

A dose of 4,000 to 4,500 r to the midplane of the pelvis is delivered in 6 weeks by means of external irradiation utilizing anterior and posterior portals. This treatment is immediately followed by intracavitary radium application to deliver a dose of 4,000 to 4,500 gamma roentgens to Point A. Spontaneous abortion usually

 $T_{ABLE\ VIII}$ distribution of cases at time of diagnosis in the pregnant and post partum groups

Stage	_	Post Partum	Total
I	17	10	27 (41%)
H	9	15	24 (36%)
III		12	12 (18%)
IV		3	3 (4%)
	attan canage	Manager 1. and	
Total	26	40	-66 (100%

takes place during the external irradiation (between 3 to 6 weeks after the external irradiation is started) in those cases treated during the first and second trimesters of pregnancy. Of a total of 17 patients who were in this group, only 1 failed to abort, and hysterotomy had to be done 10 days after external therapy was completed. Fetal death was evident at this time roent-genographically as well as clinically.

RESULTS

Carcinoma of the cervix associated with pregnancy has been reported to have a worse prognosis than carcinoma of the cervix uncomplicated by pregnancy. 11,14,23,26 Although the over-all 5 year survival in our series seems to be poor (Table 1x), if only those cases which had completed treatment (external irradiation followed by intracavitary radium) are analyzed, these results are not significantly different from our results with carcinoma of the cervix not associated with pregnancy. In our series, 10 patients abandoned their radiotherapy treatment at the beginning of the course and 9 of these died of disease; 6 of these cases had an early favorable stage. Three cases were treated surgically elsewhere and referred to our institution for postoperative radiotherapy of presumptive residual disease; all of these were dead at the end of 5 years. Table 1x shows our results with

Table IX

CARCINOMA OF THE CERVIX AND PREGNANCY
FIVE YEAR SURVIVAL IN RELATION
TO TREATMENT*

Treatment	Pregnant	Post Partum	Total
Complete	***************************************	**************************************	
Radiotherapy	5 of 7	7 of 19	12 of 26
Incomplete			
Radiotherapy	1 of 3	o of 7	1 of 10
Surgery	0 of 2	o of 1	o of 3
Not Treated	0 of 1		o of 1

Total	6 of 13	7 of 27	13 of 40

^{*} Forty of 66 cases were suitable for analysis of 5 year survival.

Table X

FIVE YEAR SURVIVAL IN RELATION TO STAGING AND TREATMENT

Treatment	I	11	Ш	IV
Complete Radiotherapy	5/7	5/13	2/6	************
Incomplete Radiotherapy	1/3	0/3	0/2	0/2
Surgery	0/2	O/ I	- Annual	
Not Treated	0/1	Malanand		Manager,
	***************************************	#1.1.1.1		
Total	, 0	5/17		,

patients of carcinoma of the cervix associated with pregnancy whether the disease was diagnosed during pregnancy or in the 1 year postpartum interval. Postpartum cases had a worse prognosis than pregnant patients (37 per cent vs. 71 per cent); however, we must take into consideration that the former group contained more advanced cases.

The results of treatment related to clinical stage of the disease are presented in Table x. The 5 year survival rates in patients receiving complete radiation treatment were 5/7 (71.4 per cent) in Stage 1; 5/13 (38.4 per cent) in Stage II; and 2/6 (33 per cent) in Stage III.

Adenocarcinoma of the cervix has been reported to have a less favorable prognosis than epidermoid carcinoma.⁴⁰ Our series included 2 cases of adenocarcinoma of the cervix associated with pregnancy, I was Stage I and the other Stage II and both were alive and free of disease for 5 years or more.

IS VAGINAL DELIVERY CONTRAINDICATED?

Vaginal delivery in patients with carcinoma of the cervix associated with pregnancy has been considered contraindicated by most authors (Table XI).

Heyman¹² was one of the first to recommend vaginal delivery in pregnant women with carcinoma of the cervix. After treating 9 cases in the third trimester by cesarean section followed by radical surgery and radiotherapy, only 1 of such cases survived

Table XI

FIVE YEAR SURVIVAL IN RELATION TO MODE OF DELIVERY

Stage -	Vaginal Delivery		Abdominal Delivery	
	No. of Cases	vors	No. of Cases	Survi- vors
I	11	5	2	1
11	13	5	4	0
Ш	8	2	R. A. C.	where
IV	2	0	No. 100	www
	encourage.		********	
Total	34	12	6	1

5 years. Gustafsson and Kottmeier¹¹ reviewed Heyman's material and added 6 new cases where delivery occurred spontaneously in 2 patients and both were living and symptom free more than 5 years; only 1 of the other 4 cases survived over 5 years.

Petersen³⁰ reported 3 cases treated during the third trimester by means of a radium plaque and allowed to deliver vaginally, 2 of which remained free of disease at the end of 5 years.

Waldrop and Palmer,⁴⁰ reviewing the Roswell Park Memorial Institute series, found that those patients who were delivered vaginally had "a better 5 year cure rate" than those who had a cesarean section (45.8 per cent for those delivered vaginally versus 17.5 per cent for those by cesarean section or hysterotomy).

Table XI shows the 5 year survival in relation to the mode of delivery. The group of cases delivered vaginally includes patients in the 3 trimesters, while those submitted to abdominal delivery were all in the third trimester or postpartum period. Even though the number of patients in our series is small, the survival rate in patients who were delivered vaginally is better than the survival rate of those delivered abdominally.

DISCUSSION

The incidence of carcinoma of the cervix associated with pregnancy is low, with an

average of 1 case per 2,500 pregnancies or 2 to 3 cases per year in a busy cancer center. Because of the rarity of this condition, no one can consider himself an expert in the management of these cases. When the problem arises, the decision must rest on our evaluation of the factors concerned with the outcome of the mother and the fetus.

In the first trimester of pregnancy, there seems to be no question of what to do, as immediate treatment is mandatory. Second trimester cases, in our opinion, should be treated as soon as possible without consideration of the fetus if we want the patient to have the best chances of survival.

Third trimester patients may motivate considerable discussion as to what to do when the fetus is not viable. To wait for 2 or 3 weeks is perfectly acceptable without significant worsening of prognosis; but a longer wait may be hazardous.

We do not feel that one should wait for a fetus to become viable if it is not already considered to be viable at the time the diagnosis is established. The question of viability is probably the most difficult decision to reach, but it should be decided promptly so that the treatment can proceed.

Radium treatment of the cervix with the vaginal component only has been practiced by some workers, but we consider it potentially dangerous to the baby. Consequently, we prefer to see the uterus emptied by cesarean section, and then to start external radiation therapy followed by intracavitary radium. In our cases the administration of external radiation to the pregnant uterus resulted in a dead fetus which was aborted before the external radiation was completed. Only 1 of 17 patients failed to abort spontaneously during or after external irradiation.

Vaginal delivery of the baby in the presence of carcinoma of the cervix has been considered dangerous because of the possibility of massive hemorrhage, infection, and rapid dissemination of the tumor. On theoretical grounds, we feel that vaginal delivery should be avoided. However, if this

event should occur, and it is not always under the control of the physician, it does not necessarily worsen the prognosis. In support of this contention, we have our experience with 34 cases of carcinoma of the cervix who gave birth vaginally; 12 patients (35 per cent) survived 5 years or longer, showing that a significant number can overcome the risk involved.

We have observed that the stage of the disease is more advanced when diagnosed post partum than during pregnancy. It is possible that the vaginal delivery may have contributed to the extension of the disease. However, it is also evident that vaginal bleeding during pregnancy attracts the attention of the patient and the physician more than when it occurs in the postpartum period. The average duration of symptoms in the pregnant group was 3.7 months while in the postpartum cases it was 5.5 months.

It appears that pregnancy in patients with carcinoma of the cervix uteri occurs only in an early stage of the evolution of the neoplasm. Conception is hindered or prevented by an existing advanced tumor.

From our experience we have concluded that the prognosis of carcinoma of the cervix in the pregnant patient is not worse than in the nonpregnant woman with the disease.

When carcinoma of the cervix is discovered during pregnancy rather than in the postpartum period, the tumor is less extensive and consequently has a better prognosis. Therefore, we advocate exfoliative cytology examinations of the cervix and the vagina of all pregnant women, particularly at the time of the initial prenatal visit to the physician. This test should be repeated at the postpartum visit.

SUMMARY

- 1. A group of 66 cases of carcinoma of the cervix associated with pregnancy seen at the I. González Martínez Oncologic Hospital in a 23 year period has been reviewed.
 - 2. Irradiation is considered the treat-

ment of choice. The results obtained are comparable to those obtained with lesions of similar stage not associated with pregnancy.

- 3. First and second trimester cases should be submitted to pelvic irradiation without consideration of the fetus. Third trimester patients should be promptly delivered by cesarean section and then irradiated.
- 4. Thirty-four patients with carcinoma of the cervix gave birth vaginally and 12 (35 per cent) survived 5 years or longer, showing that a significant number can overcome the risk involved.

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A CRITICAL EVALUATION OF THE ROENTGENOLOGIC EXAMINATION OF PATIENTS WITH CARCINOMA OF THE CERVIX*

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THE roentgenologic examination is a major component of the evaluation of the patient with carcinoma of the cervix. Chest roentgenography, intravenous or retrograde pyelography, cystography, examination of the colon, bone survey, pelvic vascular studies, pelvic lymphography, and special examinations may be included in various combinations.

This report, an evaluation of 10 years' experience in the roentgenologic examination of patients with histologically invasive carcinoma of the cervix, is an attempt to assess the efficacy of this major effort.

MATERIAL

In 300 patients, the roentgenograms and/or their official interpretations were reviewed. These included more than 90 per cent of patients with a diagnosis of invasive carcinoma of the cervix at the King County Hospital between 1952 and 1962 and all patients with the same diagnosis at the University Hospital between 1959 and 1962. Two hundred and twenty-four patients were untreated at the time of initial examination. Distribution by League of Natients was: Stage I—83 patients; Stage II—63 patients; Stage III—40 patients; and Stage IV—38 patients.

Seventy-six patients had been treated elsewhere prior to initial evaluation in our hospitals. Fifty-seven of these 76 patients had uncontrolled tumor comparable in extent to Clinical Stages III or IV. The age range of the entire group was 25–89 years with 30 per cent over 70 years and 5 per cent under 30 years.

EVALUATION OF EXAMINATIONS A. CHEST ROENTGENOGRAM

All 300 patients had roentgenographic examination of the chest during initial evaluation. Only a single posteroanterior roentgenogram was obtained in the majority. Five (2.2 per cent) abnormal chests, considered tumor-related, were found in the 224 patients not previously treated. Two patients had bilateral pulmonary parenchymal nodules, considered to represent metastases (Fig. 1, A and B). Two patients had parenchymal infiltrates with ipsilateral pleural effusions containing neoplastic cells (Fig. 2, A and B). One patient had hilar lymphadenopathy. All 5 patients had extensive intrapelvic tumor and 2 had supraclavicular lymphadenopathy, abling a clinical staging of IV in 3 patients and III in 2, exclusive of the abnormal findings in the chest roentgenograms (Table 1).

In 13 (6 per cent) of the 219 patients with normal pretreatment chest roentgenograms, tumor-related abnormality eventually was detected. There were bilateral pulmonary parenchymal lymph nodes in 7, and hilar lymphadenopathy, parenchymal infiltrations, and ipsilateral pleural effusions in the others. In 8 patients, the intrathoracic metastases were detected within 12 months of initial evaluation and treatment, while in the other 5 patients, the lesions were detected 2 (2), 3 (1) and 6 (2) years after treatment (Table II). Therefore, in this group of 224 patients, hematogenous and lymphatic intrathoracic metastases were detected with comparable frequency and sometimes occurred in the same patient. There was no documented pulmonary

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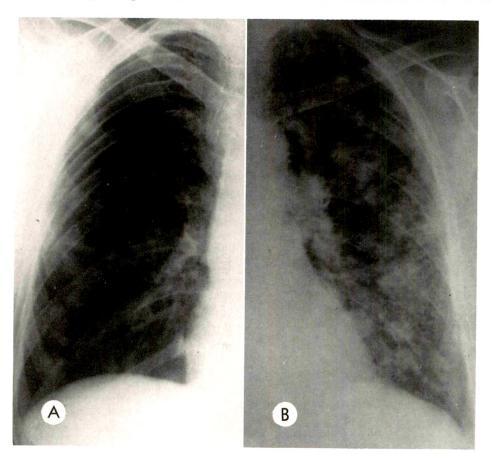


Fig. 1. (A and B) Nodular pulmonary parenchymal metastases.

 $T_{ABLE\ I}$ abnormal pretreatment chest roentgenograms $(224\ primary\ cases)$

Case No.	Physical Findings	Clinical Stage Exclusive of Chest	Surviva
I	"Frozen pelvis" with vesicovaginal fistula, no intravenous pyelogram	o- IV	ı wk.
2	Fixed right pelvis, right supraclavicular lymphadenopathy, intravenous pyelogram normal	IV	8 mo.
3	"Frozen pelvis," abdominal mass, right supraclavicular lymphadenopathy, no intravenous pyelogram	IV	ı wk.
4	Fixed right pelvis, involvement of lower vagina, intravenous pyelogram normal	III	ı mo.
5	Bilateral parametrial fixation, unilateral ureteral obstruction, ? involvement of base of bladder (cystoscopy)	III	3 mo.

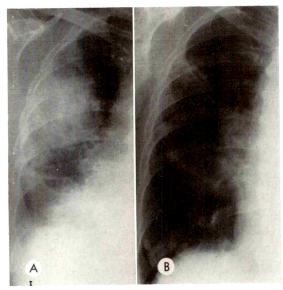


Fig. 2. (A) Parenchymal infiltration and pleural effusion containing neoplastic cells, clearing after local irradiation (B).

lymphangitic spread. All intrathoracic metastases were in patients with extensive pelvic tumor.

Of 23 adequately followed patients (from the entire series) with intrathoracic metastases, 19 died with tumor within 1 year, 2 died with tumor within 2 years, and 1 died with tumor within 3 years after detection of the intrathoracic lesions. A single patient with a hilar mass proved at thoracotomy 11 years after radiation therapy of the primary lesion, is alive without symptoms but with an abnormal chest roentgenogram 5

TABLE II

POST-TREATMENT DEVELOPMENT OF ABNORMAL
CHEST ROENTGENOGRAMS

Pre- treatment Stage	No. Developing Intra- thoracic Metastases	Total Treated in Stage	Interval from Treatment to Detection
I	4	83	6 mo3 yr.
II	3	63	4 mo6 yr.
III	3	40	10 mo6 yr.
IV	3	38	9 mo2 yr.
	13	224	

years after mediastinal irradiation (Fig. 3, A and B).

Only two incidental lesions of consequence were recorded: one patient had previously undiagnosed cavitary pulmonary tuberculosis and another had unsuspected carcinoma of the bronchus proved at autopsy.

B. INTRAVENOUS PYELOGRAM

Intravenous pyelograms were obtained in 217 of the 224 patients evaluated for initial treatment. Forty-five (21 per cent) of the examinations were abnormal because of deviated ureters, hydronephrosis or nonvisualization of the urinary outflow tract. These abnormalities have been related to clinical staging of disease in Table III.

A few patients were excluded from this tabulation because unilateral nonvisualization could be related to previous nephrectomy. The single abnormality in a clinical Stage I patient was attributed to uterine fibroids. This patient survives. In no other instance was an abnormal pyelogram an isolated finding unrelated to palpable extension of tumor.

Following treatment in our institution, 24 patients (11 per cent) with initially normal pyelograms eventually were found to have tumor-related abnormality. However, not all patients with uncontrolled tumor had serial post-treatment pyelograms. Abnormalities in this group were detected at the following post-treatment intervals: 7 of 24 within 4 months; 12 of 24 within 10 months; 19 of 24 within 24 months; and others at 2, 3, 4, and 6 years.

Thirty-four of 63 (54 per cent) patients previously treated elsewhere had abnormal pyelograms on initial evaluation in our hospitals.

In all post-treatment patients, ureteral abnormalities could be related to palpable pelvic tumor except in those 3 patients where the ureteral abnormality first appeared shortly after radical pelvic surgery.

Pyelographic abnormalities are ominous. Of 42 adequately followed patients with abnormal pretreatment pyelograms, only 4

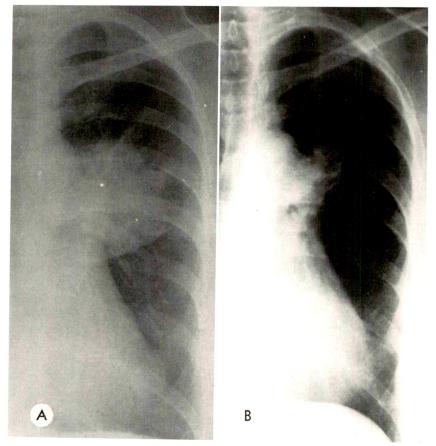


Fig. 3. (A) Biopsy-proved hilar mass detected 11 years after treatment of carcinoma of the cervix.

(B) Appearance 2 years after mediastinal irradiation (now 5 years and unchanged).

(10 per cent) are living without evidence of tumor (excluding the patient with fibroids). This survival rate of patients with tumor-related pyelographic abnormality is lower

than in some reports in the literature, and may be related to the ineffectiveness of treatment early in this series.

Four patients had transitory objective

Table III
ABNORMAL PRETREATMENT PYELOGRAMS

Roentgenologic Abnormality	Relationship of Pyelographic Abnormality to Clinical Staging						
- Toomigenologic Honormanty	I	II	III	IV	Total		
Deviated ureter	0	3	I	Ţ			
Unilateral hydronephrosis	I	0	7	3	3		
Bilateral hydronephrosis	0	0	2	6	8		
Unilateral nonvisualization	0	I	3	11	1.5		
Bilateral nonvisualization	0	0	2	4	6		
	I	4	15	25	45		
Γotal no. of patients in each stage	83	63	40	38	224		

Table IV Survival periods of patients with abnormal pretreatment pyelograms

	Interval: Examination to Death (in years)						
Abnormality	Less than	1-2	2-3	3-4	Lost		
Deviated ureter	2	I	0	0	2		
Inilateral hydronephrosis	5	2	4	0	0		
Bilateral hydronephrosis	7	0	I	0	0		
Inilateral nonvisualization	8	3	I	2	1		
Bilateral nonvisualization	6	0	0	0	0		
	28	6	6	2	3		

improvement of pretreatment pyelographic abnormality following radiation therapy. Two patients with unilateral nonvisualization of the urinary outflow tract regained function following pelvic irradiation, but died with uncontrolled tumor, I and 4 years post treatment. Two patients had improvement of unilateral hydronephrosis but died with uncontrolled tumor, I and 2 years

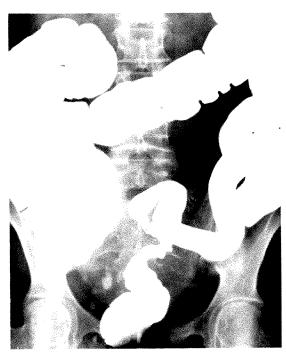


Fig. 4. Tumor-produced deformity of the rectosigmoid in a patient with extensive intrapelvic tumor.

after treatment. The survival period of these patients with tumor-related pyelographic abnormality is short (Table 1V).

Of those initially treated elsewhere, all with pyelographic abnormality died with uncontrolled tumor (93 per cent within 1 year and 97 per cent within 2 years of detection of the abnormality).

C. BARIUM ENEMA

The colon was examined in 149 patients prior to treatment. In 11 (7 per cent) there was suspected involvement of the bowel wall by tumor or encroachment on the lumen by pressure from tumor. After treatment, similar findings were reported in 7 other patients at intervals of less than 12 months (4 of 7), 1½ years, 2 years and 7 years. These roentgenographic findings always could be related to palpable intrapelvic tumor. However, the site, extent and description of the bowel involvement, suspected from clinical findings, could not be documented consistently by any other method of examination (Fig. 4).

A finding of compromise of the colon by tumor is important in planning care of these patients, for in many instances palliative colostomy should be the initial therapeutic procedure.

Involvement of the bowel wall is a grave prognostic finding. In no instance did a tumor-involved colon return to normal appearance following treatment. Nineteen

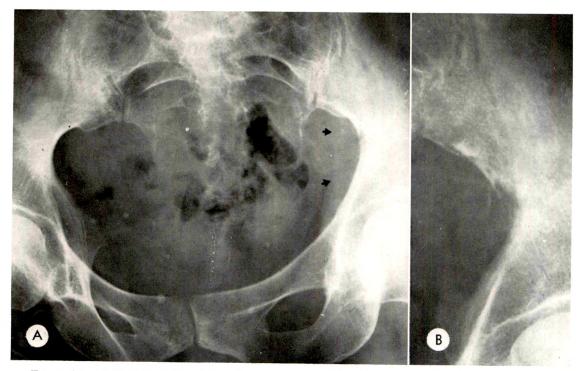


Fig. 5. (A and B) Destruction of ilium (arrows) causing pain for several months prior to diagnosis.

of 21 patients (including those treated elsewhere), adequately followed, died within 1 year of the finding of tumor-related abnormality of the colon.

D. SKELETAL SURVEY

Examination of bone was based on inclusion of ribs, shoulders and thoracic vertebrae (anterior projection) on chest roentgenograms of all 300 patients; on visualization of the pelvis, hips, and lumbosacral vertebrae (anterior projection) on pyelograms or other studies in 290; or on a "skeletal survey" including thelateral roentgenogram of the skull, entire vertebral column, pelvis, ribs, humeri and femora in 87 patients.

In the group of 224 patients evaluated for initial treatment, a single bone lesion attributed to tumor was found. This lesion, in the ilium of a patient with clinical Stage IV tumor, was preceded for several months by localized pain (Fig. 5, A and B).

Of special 7 interest is the "skeletal

survey" obtained in 87 patients prior to treatment. Failure to detect a single lesion during this clinical trial resulted in abandonment of the procedure.

Following treatment in our institution, 8 patients (3 per cent) developed bone metastases, documented on roentgenograms, at post-treatment intervals of less than 12 months (5 of 8); less than 18 months (6 of 8); and at 2 and 6 years.

Of the 76 patients evaluated after treatment elsewhere, 12 eventually had roentgenographic documentation of metastases to bone.

The total of 32 detected bone lesions in 21 patients was distributed as follows: lumbar spine—10 (Fig. 6, A and C); pelvis—8 (Fig. 7, A and B); femur—5 (Fig. 8A); sacrum—3; thoracic vertebrae—3 (Fig. 6, A and B); scapula—1; rib—1; and tibia—1 (Fig. 8B). No skull lesions were noted in 87 patient examinations. The lesions were predominantly lytic. All patients with detected bone lesions had uncontrolled pelvic tumor.

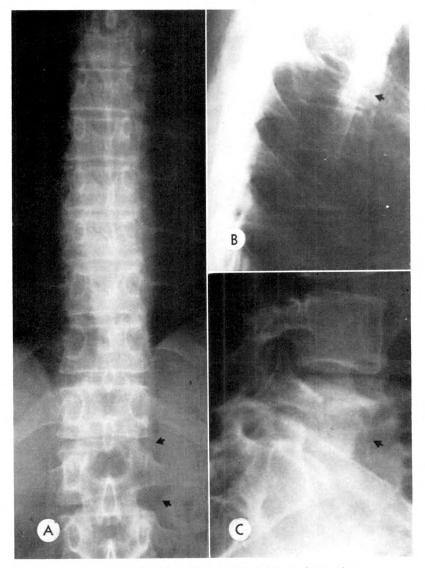


Fig. 6. (A, B and C) Vertebral metastases (arrows).

All detected lesions were heralded by localized pain for periods of I month to I year.

Of the 19 patients adequately followed, 17 died with tumor within 1 year of detection of the bone lesions.

E. OTHER EXAMINATIONS

There has been no useful experience with pelvic vascular or lymphatic studies in this series.

CONCLUSIONS

1. In patients with invasive carcinoma of the cervix, the incidence of abnormalities detected by roentgenologic examination can be related to the extent of tumor on physical examination. In no instance in this series was unexpected distant spread of tumor found in the pretreatment evaluation of patients with clinical Stage I or II disease, based on physical examination.

2. Spread of tumor detected by chest roentgenography, pyelography, colon examination or bone survey is a grave prognostic sign. All patients (except 1) with detected tumor-produced abnormalities in the thorax, colon or bone died with uncon-

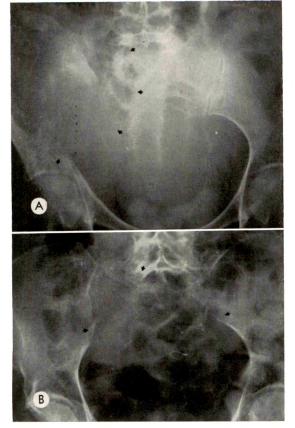


Fig. 7. (A and B) Destruction of bony pelvis (arrows) in patients with extensive intrapelvic tumor.

trolled tumor, usually within the year following detection. Abnormalities on the pyelogram can be produced by limited parametrial extension of tumor. A modest survival rate can be expected in this group.

3. Pyelography is the most helpful roentgenologic examination in the pretreatment evaluation of patients with carcinoma of the cervix. Findings on examination of the colon and chest have been useful in manage-



Fig. 8. (A and B) Distant metastases to femur and tibia.

ment of these patients. On the basis of 87 pretreatment patient evaluations, a bone survey does not seem a useful procedure.

4. Incidental findings, unrelated to tumor, were of low incidence but, occasionally proved important in the management of the patient.

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HORMONAL EXCRETIONS IN PATIENTS WITH CARCINOMA OF THE CERVIX*

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THE development of the female genitalia and their maintenance in normal condition and function depend upon the presence of estrogen. In suitably inbred mice, administration of massive doses of estrogen leads to development of carcinoma of the cervix but whether continuous or excessive administration of this hormone is responsible for development of cervical carcinoma in man is not known.

This disease appears to have a higher frequency in certain ethnic groups; it is more prevalent in Negro women than in white women¹ and definitely less prevalent among Jewish women than other women. The quality of obstetric care and the number of pregnancies also appear to influence the chances of development of cervical carcinoma.

Despite its obviously endocrine-related background, cancer of the cervix has not been shown to respond satisfactorily to changes in hormonal environment as do cancers of other hormonally regulated tissues, such as the endometrium, the breast and the prostate; and although physically and functionally the uterine cervix is a hormonally affected end organ, there are remarkably few observations on the hormonal background of patients with this disease. Therefore, an attempt was made to determine whether patients with cervical carcinoma had abnormal urinary hormonal excretion patterns.

MATERIAL AND METHOD

Urinary hormonal excretion studies were carried out on 249 women with histologically verified carcinoma of the cervix seen in the Department of Therapeutic Radi-

ology at Charity Hospital of Louisiana in New Orleans during the 3 year period beginning August 1, 1961. These studies are continuing and this report represents only preliminary observations. Since most patients (143 or 57.4 per cent) are still alive, our observations cannot be related, other than casually, to the duration of their survival. The follow-up periods ranged from a few months to 3 years. Most patients who are dead were older patients with advanced stages of the disease.

Determinations by methods previously described² were made of the following urinary hormonal excretions: creatinine, creatine, 17-ketosteroids, gonad-stimulating hormone, luteinizing hormone, formaldehydogenic corticoids, Porter and Silber chromagens, urinary calcium, and blue tetrazolium (Table 1). All determinations were obtained on a 24 hour urine sample collected before radiation therapy from each of the 249 patients. All patients have been under continuous observation.

Figure 1 shows the age distribution of the 249 patients. The proportion of women older than 55 years is definitely larger than previously observed by us—only 37 per cent from 1938 to 1952¹ as contrasted with more than half the patients in this study.

RESULTS

In Table 1 the average determinations obtained on the patients according to the stage of the disease are listed; most patients (181 or 72.7 per cent) had Stage II or Stage III disease. In general, there was a decrease in urinary creatinine excretion with advancing disease; a decrease in 17-ketosteroids with Stages III and IV; a pro-

^{*} Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8-10, 1965.
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This study was supported by Grant T-103 from the American Cancer Society, Inc.

	No. of Pa- tients	Creatinine gm./24 hr.	Creatine gm./ 24 hr.	17-Keto- steroids mg./ 24 hr.	lating Hormone	Formalde- hydogenic Corti- coids mg./DOC/ 24 hr.	ing Hormone	Calcium	P and S Chroma- gens mg./ 24 hr.	Blue Tetra- zolium mg./ 24 hr.
Stage I	53									
Average ± s.D.		0.84 ±0.17	0.08 ±0.06	7.0 ±2.2	49 ±31	0. 24 ±0.13	550 ±925	76 ±29	0.22 ±0.06	1.23 ±0.28
Stage II	94									
Average	74	0.81	0.09	7.4	8c	0.47	136	82	0.28	1.31
±s.d.		±0.58	±0.08	±2.4	± 84	±0.36	± 49	±49	±0.23	±0.49
Stage III	87					-				
Average	•	0.70	0.07	5.6	79	0.34	132	84	0.25	1.05
\pm s.d.		±0.23	±0.05	±1.8	±77	±0.15	±142	±47	±0.09	±0.26
Stage IV	15									
Average	-	0.52	0.07	5.4	44	0.32	95	60	0.26	1.16
\pm s.d.		±0.21	±0.05	±2.8	±56	±0.32	±50	±68	±0.18	±0.47

nounced decrease in gonad-stimulating hormone and luteinizing hormone in Stage IV; and a slight decrease in calcium in Stage IV.

Figure 2 shows average excretion values of creatinine according to stage of the disease in both living and dead patients compared with the normal values for premenopausal and postmenopausal women as established in the laboratory of the Section of Endocrine Research of the Alton Ochsner Medical Foundation. The creatinine values are not only lower than the normal values but they are also lower for

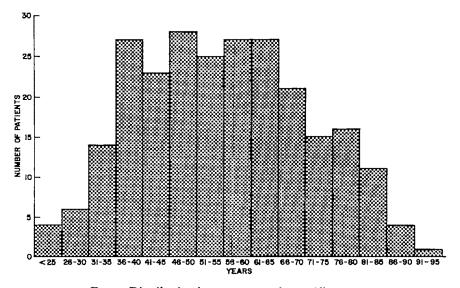


Fig. 1. Distribution by age; 249 patients. All stages.

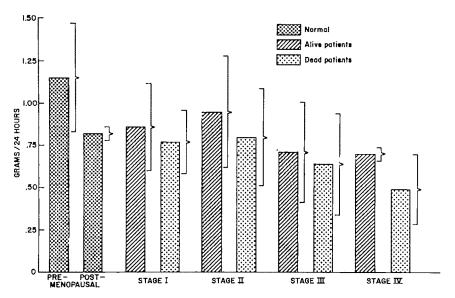


Fig. 2. Creatinine excretions. Average values by stages.

the dead patients than for those still living.

Figure 3 shows the 17-ketosteroid excretion values. Figure 4 depicts graphically the average excretion values of gonadstimulating hormone as measured by mouse uterine weight. These are strikingly below the normal for postmenopausal women and much lower than expected. The patients who have died had even lower values than those still living. Such grouping according to age as has been possible so far would indicate that most of these patients

should have high postmenopausal values. Reduction in gonadotrophin excretion has been observed in patients with carcinoma of the breast but not as great as that which occurred in the patients with cervical carcinoma. The mechanism of this hormonal alteration has not been determined, but in future studies a search will be made for antigonadotrophins in the urine.

In the excretion of luteinizing hormone (Fig. 5) as measured by the ventral prostate method in the hypophysectomized

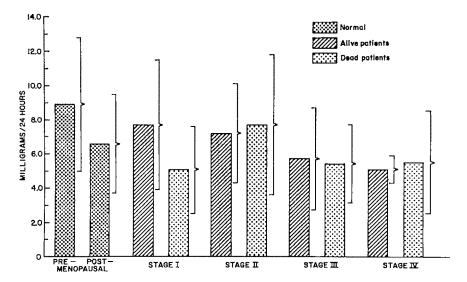


Fig. 3. 17-ketosteroid excretions. Average values by stages.

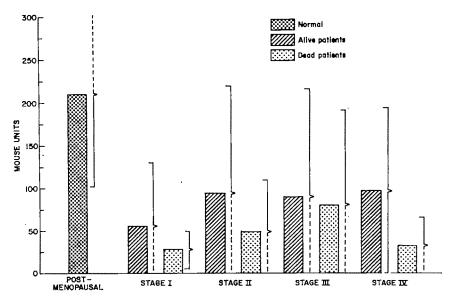


Fig. 4. Gonad-stimulating hormone excretions. Average values by stages.

immature male rat, all patients with cancer of the cervix except those with Stage I had much lower than normal values. Although in the 3 higher stages the patients were mostly of postmenopausal age, they had little or no excretion of luteinizing hormone.

Excretions of creatine, formaldehydogenic corticoids, urinary calcium, Porter and Silber chromagen and blue tetrazolium (the last two a measure of urinary corticoids) are not significantly different from the normal values and there were no positive findings in any stage of cervical cancer.

The outstanding observation in this preliminary study is that these patients with carcinoma of the cervix had considerably less excretion of urinary gonad-stimulating hormone than would be expected for their ages. As these patients are followed long

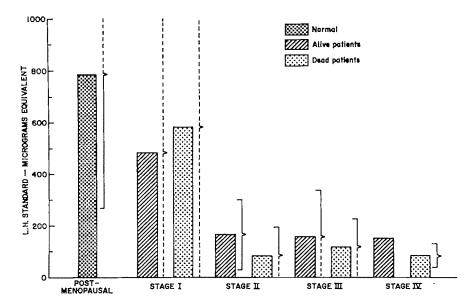


Fig. 5. Luteinizing hormone excretions. Average values by stages.

enough to acquire significant survival statistics, an attempt will be made to correlate the results with the various parameters known to affect the endocrine excretion, the response to radiation, or both. These factors include, among others, menstrual status and whether or not the urogenital tract is impaired.

SUMMARY

A study was undertaken to determine whether patients with carcinoma of the cervix have abnormal urinary hormonal excretion patterns. Determinations were obtained in 249 women with various stages of carcinoma of the cervix during a period of 3 years. A decrease in urinary creatinine

and 17-ketosteroids was noted in patients with advancing stages of the disease. A decrease in excretion of gonad-stimulating hormone was observed, greater than that to be expected for the ages of the patients.

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RADIATION THERAPY AND SURGERY IN THE TREATMENT OF CARCINOMA OF THE BLADDER*

UNIVERSITY OF MARYLAND EXPERIENCE

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THE treatment of cancer of the bladder by either radiation therapy or surgery has never been entirely satisfactory. Experience with preoperative irradiation and surgery in the treatment of cancer in other sites has encouraged us in our search for an improved therapeutic approach. Through a cooperative effort of the Divisions of Urology and Radiation Therapy of the University of Maryland, such combined treatment was started with isolated cases of bladder cancer where recurrent or residual tumor was present after irradiation and has in recent years evolved into a more systematic study (Table 1).

METHODS

Patients with the diagnosis of bladder cancer were subjected to an investigation which included roentgenography, biopsy, and bimanual examination under anesthesia. Biopsy specimens were examined for evidence of muscle involvement and histologically graded. All cases were staged clinically following as closely as possible Marshall's modification⁶ of the Jewett and Strong⁵ classification prior to the commencement of any therapy.

Cobalt 60 teletherapy was prescribed for all patients except those with Stage O, well differentiated Stage A, or Stage D₂ tumors. Cases with Stage A tumors were included if poorly differentiated or if recurrent after multiple resections or fulgurations. If extensive fulguration had been carried out, a period of 3 to 4 weeks was allowed to elapse before institution of radiation therapy. Anemia was corrected by blood transfusions, and patients with evidence of urinary tract infection were

Table I

COMBINED SUPERVOLTAGE IRRADIATION
AND TOTAL CYSTECTOMY

Males 24 Females Stage Prior to Therapy A-- 5 B-18 C-3Histology Transitional Cell Carcinoma Grade 1-2 Grade 11-7 Grade III-10 Grade IV-2 Ungraded—3 Adenocarcinoma-1 Squamous Cell Carcinoma—1 Undifferentiated-1

given antibiotics. One patient with bilateral hydronephrosis had a cutaneous ureterostomy before irradiation.

The plan of irradiation was for a dose of 6,000 rads to be delivered to a volume which encompassed as a minimum the entire bladder in 5 to 6 weeks using cobalt 60 teletherapy.1 For well differentiated tumors without extravesical extension, a dose of 6,000 rads in 5 to 6 weeks was delivered using a rotational technique. In the cases with poorly differentiated tumors, extravesical extension, marked muscle infiltration (grossly palpable tumor), or previous cystotomy, treatment was directed using a three portal technique to the entire pelvis which received a dose of 4,000-4,500 rads at the rate of 1,000 rads per week, followed by rotational therapy to a total dose of 6,000 rads to the entire

^{*} Presented at the Forty-seventh Annual Meeting, American Radium Society, New Orleans, Louisiana, April 8-10, 1965.

Table II
OPERATIVE INDICATIONS AND PREOPERATIVE FINDINGS

	No. of Patients	Positive Operative Specimen	Negative Operative Specimen
Positive Biopsy (postirradiation)	10	6	4
2. Gross Visible Tumor	3	3	0
3. Persistent Bleeding without Biopsy or	_	_	
Negative Biopsy	3	3	0
4. Cystitis with Calcification or Reduced			
Capacity—No Demonstrable Tumor	4	0	4
5. As Part of Planned Combined Therapy, Even	•		
with Negative Biopsy	7	5	2

bladder and any extravesical extension. With one exception, the actual doses ranged from 4,720 to 6,500 rads. In I case treatment was stopped after 3,200 rads because of marked dysuria, and another patient required II weeks to receive 6,500 rads because of intercurrent illness.

Cystectomy was carried out whenever possible after an interval of I to 3 months, although some patients originally refused surgery after their irradiation, and the cystectomy was carried out only when the presence of active neoplasm or severe symptoms forced acceptance of the procedure. The interval between irradiation and surgery, therefore, varied from 33 days to 42 months, although since 1961 most patients have been operated upon within 3 months of the completion of radiation therapy (Table II). A number of patients was never operated upon following radiation therapy because of the complete disappearance of tumor and symptoms. Five patients with Stage A tumors prior to irradiation underwent cystectomy. One had gross residual tumor, 2 had positive biopsies post irradiation, and 2 had contracted bladders.

The 27 patients reported here all had total cystectomy without pelvic lymphadenectomy. Urinary diversion was accomplished in 4 cases by ureterosigmoid anastomosis, in 5 cases by ureterocutaneous anastomosis, and in the remaining 18 cases by uretero-enterostomy with formation of an isolated ileal loop. This was usually

carried out as a one stage procedure, although I patient had cutaneous ureterostomy performed prior to radiation therapy and in 4 other cases a two stage procedure was used.

COMPLICATIONS

By the careful application of the principles previously reported, severe radiation reactions have been reduced to a very low number and in only I case was radiation therapy discontinued prematurely on this account. No undue technical difficulties were encountered at surgery.

Twelve of the 27 patients had postoperative complications, and in 6 cases these were fatal (Table III). The commonest complication, occurring in 6 cases, was leakage of the anastomosis or bowel fistula and this proved to be fatal in 5 of the 6. One patient died 7 months after surgery of

Table III

COMPLICATIONS OF POSTIRRADIATION CYSTECTOMY

Type of Complication	Nonfatal	Fatal
I. Leakage of Anastomosis,		
or Bowel Fistula with or		
without Peritonitis	I	5
2. Bowel Obstruction	I	0
3. Pelvic Peritonitis	I	0
4. Pelvic Abscess without		
Fistula	2	0
5. Osteitis Pubis	3	0
6. Wound Dehiscence	I	0
7. Serum Hepatitis (blood)	0	I

Note: Twelve patients had a total of 15 complications.

Table IV

COMPLICATIONS OF POSTIRRADIATION CYSTECTOMY

Length of Interval	No. of Patients	No Complications	Nonfatal Complications	Fatal Complications
Less Than 9 Weeks	8	5 (63%)	2 (25%)	1 (12%)
Longer Than 9 Weeks	19	10 (53%)	4 (21%)	5 (26%)

Note: Interval between completion of irradiation and surgery ranged from 33 days to 42 months.

hepatic failure secondary to serum hepatitis. There were no other fatal complications. Three additional patients required secondary surgery after varying intervals but are not listed as complications in the postoperative period: I had a revision of his anastomosis 2 years after cystectomy, another developed a colocutaneous fistula 18 months after surgery and required transverse colostomy, and a third developed ureteral obstruction 7 months after surgery, requiring revision of his uretero-ileal anastomosis and eventually died of uremia. A number of the complications arose in unirradiated tissues. In all. the incidence of complications was not markedly different from that reported in other series without prior radiation therapy;7 and it would indicate that irradiation does not increase the dangers of radical surgery with the techniques used in this study.

The complications which occurred may be correlated with a number of other

Table V

RELATIONSHIP OF COMPLICATIONS TO OPERATIVE FINDINGS

No.

	of Pa- tients	No Compli- cations	Nonfatal Compli- cations	Fatal Compli- cations
Tumor Present in Operative Specimen	17	9	2	6
No Tumor Present in Operative Specimen	Io	6	4	0

factors. When the interval between radiation therapy and surgery exceeded 9 weeks, there was an increased incidence of complications, especially of the fatal variety as shown in Table IV. No fatal complications occurred in the 10 cases in which the operative specimen was free of tumor while 6 of 17 with positive specimens died of their complications (Table v). Ten of the 18 patients originally diagnosed as having Stage B lesions had complications and 6 died thereof, 5 of the 6 of bowel complications (Table vi). Age, too, seemed to play a role, for the 5 patients over 67 years old at the time of surgery all developed complications and 3 died of them. Those below 50 years of age fared best, and those between 50 and 67 pursued an intermediate course.

RESULTS AND DISCUSSION

The ability to examine the entire bladder removed at operation and compare this with the original stage of the tumor has afforded us an excellent opportunity to evaluate the effectiveness of radiation therapy. Even though pretreatment staging is at best crude, it is obvious from an examination of Table VII that in 15 of the

Table VI

COMPLICATIONS AS RELATED TO ORIGINAL STAGE OF BLADDER CARCINOMA

Stage	No. of Patients	Nonfatal Complica- tions	Fatal Complica- tions
Α	5	I	0
\mathbf{B}	18	4	6
С	3	I	0
D	I	0	0

Table VII

CHANGE OF STAGE FROM ORIGINAL EVALUATION TO OPERATIVE FINDINGS

Original Stage (before irradiation)	N* C	Stage As Determined by Operation and Pathologic Examinatio							
	No. of Patients	Tumor Free	In Situ	F.	В	С	D		
A	5	2	1	0	2	0	0		
В	18	7	0	2	5	4	0		
C	3	Ī	0	ĭ	1	0	0		
D	I	0	0	0	0	0	I		
Totals	27	10	1	3	8	4	I		
Cases with Stage Uncha	nged		and a suppose of the	6	100 m				
Cases Free of Tumor			10						
Cases with 1 Stage More			6						
Cases with 1 or 2 Stages		it Not Tume	or Free	5					

cases the tumor was completely eradicated or caused to regress to a less advanced stage. Indeed, it was not uncommon for tumors readily palpable before radiation therapy to be completely impalpable at examination under anesthesia prior to cystectomy. In the remaining 12 cases, the tumor remained unchanged in stage in 6, and one stage further advanced in 6. While it may be argued that our original staging could be so erroneous as to account for the changes in stage found when tumor persisted to operation, the absence of tumor in the specimen in 10 cases can be accounted for only by the therapy given prior to operation.

In 10 of the 27 patients subjected to cystectomy, no tumor was found in the operative specimen, and another patient had only residual in situ carcinoma. The presence or absence of tumor could not always be predicted on the basis of preoperative examination including cystoscopy and biopsy (Table 11). Although gross visible tumor found at cystoscopy could always be histologically confirmed, 4 other cases with a positive biopsy prior to cystectomy were found to have a negative specimen. It is difficult to conceive of the entire tumor having been removed by simple transurethral biopsy. The marked inflammatory and postirradiation changes found in the operative specimen in these 4 cases may have led to misinterpretation of the biopsy specimen. In 2 cases where no tumor was apparent at operation, a single neoplastic focus was found in the subserosa by multiple sectioning. These findings of frequently unsuspected residual disease, often at some distance from the original tumor, together with the obvious difficulty of determining even at cystotomy the microscopic limits of the tumor have led us to prefer as a routine procedure cystectomy rather than segmental resection. In addition, the bladder is prone to develop new tumors with the passage of time and is best removed where an individual has already demonstrated such tumor forming potential.

Survival data have been calculated from both the date of commencement of radiation therapy and the date of surgery since the interval between the two has occasionally been long. Of the 27 patients, 13 are dead, having survived from 1 to 49 months following surgery, although all but 2 died within 16 months. Thirteen patients remain alive and free of tumor from a minimum of I year to over 4 years and I patient is alive after 13 months with a urethral recurrence. The 3 year cumulative survival is 54 per cent dated from inception of radiation therapy and 52 per cent dated from surgery. The computed 5 year survival is 39 per cent from date of irradiation and 31 per cent from date of surgery (Table viii).

TABLE VIII
SURVIVAL WITH COMBINED SUPERVOLTAGE
IRRADIATION AND TOTAL CYSTECTOMY

	From Date of Irradiation	From Date of Surgery
Three Years	54%	52%
Five Years	39%	31%

COMMENTS

As might be expected, the survival was higher when no tumor was present in the operative specimen, but, of the 17 patients with residual tumor in the bladder, 5 remain alive, 2 for over 1 year and 3 for over 2 years (Table 1x). There can be no reasonable doubt that the latter group has benefitted from the postirradiation cystectomy and that even more such patients could be cured if our incidence of fatal complications could be reduced. We must, however, justify cystectomy in the group where no tumor was found at operation. There is great difficulty in determining the presence and more especially the absence of tumor prior to cystectomy. The inaccuracy of our most complete clinical examination and the tendency of recurrent and new tumors to appear, together with the absence of fatal complications in our brief series if no tumor is, in fact, present would seem to make cystectomy a lesser evil than delay.

Past experience has indicated that neither surgery nor radiation therapy alone is sufficient to provide a desirably high cure rate with deeply infiltrating tumors of the bladder even though we know that they remain limited to the pelvis in half of the victims at the time of death. Only a more aggressive approach is likely to raise significantly the cure rate, and such an approach may well be the combination of preoperative irradiation and tectomy. The two modalities are in this condition complementary. Surgery can eradicate the local residual neoplasm in the bladder, while preoperative irradiation can reduce the bulk and extensions of the tumor, facilitating operation, for in none of these cases was it found impossible to proceed with the planned cystectomy at the time of laparotomy. In addition, by reducing the number of viable tumor cells, the all too common seeding of the operative site should be reduced, together with the number of distant metastases produced via blood and lymphatic vessels.2,3 It is highly probable that, as in carcinoma of the cervix, a high percentage of lymph nodes in the pelvis are rendered tumor free by preoperative irradiation to radical levels, although this has not been directly demonstrated in our study.

This series merely indicates the possibilities present in combined preoperative supervoltage irradiation and surgery, for such a combination may permit the cure of some cases generally considered incurable and make possible a more widely applicable approach to the treatment of bladder

Table IX
SURVIVAL FOLLOWING SUPERVOLTAGE IRRADIATION AND TOTAL CYSTECTOMY

Findings at Operation	No. of	Survival from Date of Surgery	
	Patients	Dead	Alive
Tumor Present in Specimen	17	(1 mo., 1 mo., $1\frac{1}{2}$ mo., 2 mo., 4 mo., 6 mo., 7 mo., $8\frac{1}{2}$ mo., 9 mo., 14 mo., 16 mo., 49 mo.)	5 1-2 yr2 2-3 yr3
Specimen Free 10 of Tumor		I (29 mo.)	9 1-2 yr.—3 2-3 yr.—1 3-4 yr.—2 4-5 yr.—3

cancer. While it is apparent that the interval between irradiation and surgery should not exceed 9 weeks, and probably lies between 4 and 8 weeks, the optimum interval is unknown. The merits of a one stage procedure remain to be tested against the same surgery performed in two stages. The radiation therapy might be given in doses of 2,000-4,000 rads, \$,4,8 possibly with a shorter waiting period before surgery. Such doses have the potential of eradicating some primary tumors and reducing the possibility of wound seeding or metastasis, but are unlikely to control lymph node metastases or extravesical extensions with the same effectiveness as doses of 5,000-6,000 rads. Different schemes of fractionation also deserve further investigation.

SUMMARY

Twenty-seven patients with bladder cancer were subjected to preoperative supervoltage irradiation and total cystectomy. A study of this group has yielded the following conclusions:

- 1. The preoperative evaluation of the presence or absence of tumor is inaccurate if compared minutely with the operative specimen.
- 2. It is not uncommon for recurrences or new tumors to appear in the bladder long after apparently successful irradiation.
- 3. Preoperative irradiation can eradicate some bladder tumors and in other cases reduce the bulk and extent of the tumor, thus altering the stage. All patients who were subjected to laparotomy post irradiation had resectable tumors.
- 4. Postoperative complications occurred in numbers similar to those reported in series without prior radiotherapy. Forty-four per cent of patients had complications and 22 per cent died of them. The commonest and most serious complication involved bowel or the uretero-enteric anastomosis. Complications were most frequent if the interval between irradiation and surgery exceeded 9 weeks or if the patients were of advanced age.

- 5. The combination of preoperative irradiation and total cystectomy is a feasible approach to the management of invasive bladder cancer, and would appear to offer a more favorable prognosis than either modality alone. It deserves greater use and a more complete investigation of its possibilities.
- 6. We are planning to employ this approach in a systematic manner, using preoperative irradiation in all cases of infiltrating cancer of the bladder which are easily palpable, whether limited to or beyond the bladder, provided no distant metastases are present.

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AN EVALUATION OF TREATMENT METHODS FOR LUNG CARCINOMA*

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BETWEEN May, 1955, and June 30, 1964, there were 830 patients admitted to the UCLA Center for Health Sciences hospital or to the outpatient clinics with lung cancer. Of this number, 698 were males and 132 females. Only 2 patients were lost to follow-up.

The youngest male patient was 30 years of age and the oldest 86; the average age was 59.4 years. The youngest female patient was 25 years of age, the oldest 80; the average age was 54.1 years.

The right lung was involved in 400 of the 698 males, the left lung in 282, and both lungs in 16 patients. The primary carcinoma was located in the right lung in 73 of the 132 female patients, in the left lung in 54, and bilaterally in 5 patients.

The histologic classification of the lung cancer in the males was epidermoid carcinoma in 276, undifferentiated carcinoma carcinomas, I alveolar carcinoma and the exact cell type was not given in 7 patients.

The scalene lymph node biopsy revealed metastasis in 118 of the male patients; it was negative in 153, and not done in 427 patients. The biopsy was positive in 44 of the 132 female patients, negative in 14, and not performed in 74 patients.

The survival data for the 737 deceased patients irrespective of the type of therapy are as follows:

The average survival period of the 620 deceased males was 7.39 months and 6.89 months for the 117 deceased female patients. The average survival time of the total deceased group of 737 patients was 7.31 months. The survival time was calculated from the day of surgery or from the last day of the first treatment series.

The percentage of deceased patients by year and sex is as follows:

		Males (620 deceased)	
First year 512 (82.6%)	Second year 74 (11.9%)	Third year 21 (3.4%)	Fourth year 6 (1%)	Fifth year 7 (1.1%)
		Females (117 decease	ed)	
First year 94 (80.4%)	Second year 18 (15.4%)	Third year 3 (2.6%)	Fourth year 1 (0.8%)	Fifth year 1 (0.8%)

in 250, adenocarcinoma in 90, and the exact cell type was not specified in 14 patients. The diagnosis was based on Papanicolaou smear studies and/or clinical evidence in 61 patients. Alveolar carcinoma was diagnosed in 7 male patients. In the 132 female patients, the predominant cell type was undifferentiated carcinoma in 55. Thirty-nine had tumors of the adenocarcinoma type, 30 epidermoid

For surgery or radiation therapy to be successful in the treatment of lung cancer, the primary lesion must be localized to the lung involved and/or the immediate lymphatic drainage region which is accessible to surgical removal.

Unrecognized widespread dissemination of cancer cells must occur early in the majority of the patients with lung cancer via the vascular route, the lymphatics, or

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Table I

PER CENT DISTRIBUTION OF LUNG CANCER CASES BY STAGE OF DISEASE IN CALIFORNIA, 1942–1956

Ç	No. of	Stage	Total	Per Cent of Stage Kno		Known
Sex Cas	Cases	Unknown	Iotai	Localized	Regional	Remote
Both sexes	6,666	5,588	100.0	14.9	28.8	56.3
Male	5,523	4,620	1∞.0	14.8	29.2	56.0
Female	1,143	968	100.0	15.4	26.5	58.1

both, since such a small percentage of cases are curable. The ability to grow silently is characteristic of lung cancer.

A study of 6,666 cases initially diagnosed during 1942–1956 as lung cancer and reported to the California Tumor Registry from hospitals in California revealed that only 15 per cent of the cases were diagnosed as being localized initially; 29 per cent had regional spread and 56 per cent had remote metastases (Table 1).²

The assumption was made that since 85 per cent of lung cancer patients reported in the California Tumor Registry study had regional or remote metastasis or both at the time of diagnosis, it is unlikely that symptoms precede the involvement of other tissues by an appreciable period. In the California Tumor Registry study 21 per cent of the patients with squamous cell carcinomas had localized disease, whereas only 10–13 per cent had localized disease regardless of the histologic type or sex of the patient.

There is considerable variation in the rate of growth of primary lung carcinomas in individual patients. Spratt et al.15 determined the rate of growth of 22 untreated spherical primary lung tumors from serial thoracic roentgenograms. The volume was determined from measurements of the radius of the lesions. Nine of the patients had undifferentiated carcinomas, 7 had adenocarcinomas and 6 had epidermoid lesions. With the assumption that a tumor grows at a constant rate and that the growth starts from a single cell or a small clone of cells, the age of the undifferentiated tumor was calculated to be 7.5 years; of an epidermoid carcinoma 7.8 years; and of an adenocarcinoma 22.4 years.

A similar study of the rate of growth of 41 untreated peripheral primary lung carcinomas was made by Garland et al.4 Assuming a constant rate of growth from a theoretic size of one cell, the rate of growth can be calculated from the product of the volume-doubling time and the number of volume doublings. There were 22 patients with squamous cell carcinoma, o with undifferentiated carcinoma, 7 with adenocarcinoma, and 3 patients had mixed or unclassified carcinomas. The estimated duration of the tumors from the time of inception to a diameter of 2 cm. was 25.5 years for the adenocarcinomas and 9.1 years for squamous cell carcinomas. Based on the findings of this study, they believe that, "The period of silent growth of primary lung cancers is often to be measured in decades, rather than in months or years." Collins and co-workers^{3,10} reported their observations on growth rates of human tumors and discussed the clinical applications of such data.

From his observations, Rigler^{11,12} noted that the mean time between the first roentgenographic observation and surgery is over 2 years. He has collected a large series of cases with primary lung carcinomas which were repeatedly "missed" in the interpretation of roentgenograms until the lesions enlarged considerably in size.

UNTREATED LUNG CANCER

There are several series of patients with untreated lung cancer whose survival data can be used as a baseline by which to determine the results of therapy. Garland and Sisson⁵ reported an average survival time of 3.2 months for 275 patients who

were not terminal at the time of diagnosis. Watson¹⁸ noted the average survival period of 295 deceased untreated patients with lung cancer to be 3.1 months. Shanks¹⁴ recorded the average survival time of 57 untreated lung cancer patients as 3.6 months.

INCIDENCE

The death rates from lung cancer in certain selected countries where good statistics are available reveal that England and Wales have the highest number of deaths per 100,000 population, followed by Finland, Germany and the United States. In 1955 the number of deaths per 100,000 population for lung cancer in the United States was 31.2 for males and 5.6 for females; in California there were 34.2 male deaths and 6.3 female deaths per 100,000 population.¹¹

The per cent of lung cancer cases when compared with cancer for all sites for each sex in California by time period is shown in Table 11.

EARLY DIAGNOSIS

How early is early diagnosis in patients with lung cancer? Not infrequently, patients are now being diagnosed when symptom-free and yet their tumors are found to be inoperable. Many patients are diagnosed and definitive treatment is carried out within 2 or 3 months from the onset of symptoms and they still die within a year. The earliest symptom in some patients with undifferentiated inoperable lung carcinoma producing the superior vena caval syndrome may be swelling of the face and neck. It is unusual for a patient with undifferentiated lung carcinoma causing the superior vena caval syndrome to live longer than 2 years.

Can lung cancer be diagnosed at an earlier stage? It is not probable that new techniques will be found in the near future by which lung carcinoma will be diagnosed at an earlier stage. There is no method for detecting lung abnormality which is superior to roentgen study at the present time. Considerable evidence has been pre-

Table II

PER CENT OF LUNG CANCER CASES IN CALIFORNIA

PARK			
Sex	1942-1946	1947-1951	1952-1956
Male	8.0	9.7	12.5
Female	1.6	1.9	2.2

sented by Rigler,11,12 Garland and Sisson5 and others to indicate than in many cases carcinoma of the lung develops slowly and, if the correct diagnosis could be made promptly and therapy instituted, the chances for cure would be greatly increased. If most of the lesions begin peripherally and then spread toward the hilus, early diagnosis and therapy should be effective in a relatively high percentage of cases. Retrospective studies of patients have too often revealed the presence of "overlooked" lesions. The fact that the roentgenographic findings may be present long before the patient has any clinical symptoms should encourage the development of a high index of suspicion for lung cancer in all physicians participating in the diagnosis of chest diseases.

It is not anticipated that present methods of treatment, surgery, radiation therapy, or chemotherapy will materially affect the course of this disease with its biologic inherent capacity to metastasize early and widely. If the primary lesions can be diagnosed and treated when still located peripherally, the chances for cure are reasonably good. The first successful pneumonectomy for lung carcinomas was done 32 vears ago by Graham (1933) and vet the number of patients cured by this operation still remains very small. The use of mass roentgen-ray surveys will not materially help. The greatest hope for the future will probably be in the discovery of a new chemotherapeutic agent which will either destroy the tumor cells or, when combined with radiotherapy or surgery, will make these modalities more effective in its control. The greatest emphasis should be directed to the prevention of the disease. The discouragement of cigarette smoking in high school students and the elimination

of atmospheric pollutants as much as possible should certainly be advocated.

SELECTION OF PATIENTS FOR THERAPY AND MODES OF TREATMENT

The plan of treatment in the present series was surgical exploration in all patients who were considered to be operable and who were suitable surgical candidates. For radiation therapy, the following criteria were used in the selection of patients:

- 1. Proven lung carcinoma considered to be operable, but surgery refused by the patient or when the patient was a poor surgical risk.
- 2. Residual lymph node involvement in the hilar or adjacent mediastinal region following pneumonectomy or lobectomy.
- 3. Carcinoma involving trachea or too close to the carina for definitive surgery.

A tumor dose of 1,000 to 1,500 rads weekly was delivered with a total tumor dose of 4,500 to 6,000 rads. Megavoltage therapy (cobalt 60) was used. The average tumor dose given to patients fulfilling these criteria was approximately 5,500 rads in 5 to 6 weeks.

Many of the patients who had lung carcinoma which was confined to a limited area and considered to be operable were found to be inoperable, following exploratory thoracotomy.

Patients to whom only palliative therapy could be given in the treatment of hemoptysis, severe cough, pressure on the esophagus by tumor, superior vena caval obstruction, or localized pain received tumor doses varying from 1,500 to 4,000 rads. Approximately 65 per cent of the patients received significant palliation as a result of this form of radiation therapy.

When the primary tumors are located near the hilar region and directly opposing anterior and posterior mediastinal fields (to include the adjacent involved hilar region) are used, corrective factors are not necessary in calculating the dosage. If the tumor is located in the peripheral areas of the lung, the tumor dose delivered may be

approximately 15 to 20 per cent greater unless corrective factors are utilized in determining the tumor dose.

Five hundred and four patients in this series received an average tumor dose of 5,388 rads to the thoracic spinal cord. Not one patient had symptoms suggesting spinal cord damage. One reason for the lack of spinal cord symptoms may be that most of the patients did not live long enough. Opposing treatment fields were used in all of these cases. Rather than to use techniques which might not include all of the tumor area, the high dose delivered to the spinal cord was given as a calculated risk to see if improvement in the end results could be obtained. Since no appreciable increase in end results was obtained, it was decided to give tumor doses up to 4,500 rads, and to include the spinal cord for centrally located lesions when directly opposing treatment fields are used. Oblique fields are then used to spare the cord when it is planned to give a higher tumor dose to the tumor.

Eighty male patients had thoracotomy and irradiation with an average tumor dose of 5,719 rads. Four patients are still living. The average survival time post thoracotomy was 11.4 months and post irradiation 8.1 months (Table III).

Fifteen female patients had thoracotomy and irradiation with an average tumor dose of 5,765 rads. The average survival time post thoracotomy was 8.85 months and post irradiation 6.4 months (Table IV). One hundred and twenty-one male patients received an average tumor dose of 5,504 rads. The average survival time was 8.9 months; II of these patients are still living (Table v).

Nineteen female patients had irradiation only, with an average tumor dose of 5,230 rads. The average survival time was 10 months. One patient survived 54.3 months (Table vi). If the primary lesion cannot be resected, it is believed that only a biopsy should be performed and then irradiation given. The less disturbance of the tumor bed and of the blood supply to the tumor,

TABLE III SURVIVAL OF PATIENTS (MALE) WITH LUNG CARCINOMA (May 1955-June 30, 1964)

No. of Patients	Thora- cotomy and Irradia- tion	Tumor Dose (Co ⁶⁰ or 6 mev.) 4,5 ⁰⁰ rads+	Survival (mo.) Post Thora- cotomy*	Post Irradia- tion†
Living	4	5,718	36.8	32.4
Deceased	76	5,719	10.1	6.8
Total	80	5,719	11.4	8.1
All patient	s as above ds tumor d		less than	
Living	0			
Deceased	29	3,161	5.6	5.29
Total	29	3,161	5.6	5.29

^{*} Survival calculated from day of surgery.

the better the response from radiation therapy.

Forty-two male patients had pneumonectomy plus radiation therapy with an average tumor dose of 5,516 rads. Ten of

TABLE IV SURVIVAL OF PATIENTS (FEMALE) WITH LUNG CARCINOMA (May 1955-June 30, 1964)

No. of Patients	Thora- cotomy and Irradia- tion	Tumor Dose (Co ⁸⁰) 4,500 rads+	Survival (mo.) Post Thora- cotomy*	Post Irradia- tion†
Living Deceased	2 13	4,882 5,901	5·3 9·40	3·5 6 · 90
Total	15	5,765	8.85	6.4
All patient less than Living Deceased	s as in abo 4,500 rads 0 8	_	•	3.60
Total	8	2,732	5.4	3.60

^{*} Survival calculated from day of surgery.

TABLE V SURVIVAL OF PATIENTS (MALE) WITH LUNG CARCINOMA (May 1955-June 30, 1964)

No. of Patients	of Irradiation Tumor D ents Only (Co ⁶⁰) 4,500 rad		Survival* (mo.)
Living	II	4,749	20.0
Deceased	110	5,580	7.8
Total	121	5,504	8.9
. •	s as in above 14,500 rads to	category—trea	ited with
Living	4	3,886	4.4
Deceased	86	2,744	2.2
Total	90	2,795	2.3

^{*} Survival calculated from the last day of the first treatment

the patients are still living. The average survival period post pneumonectomy was 17.9 months and 14.0 months post irradiation (Table VII). Thirty-one male patients had lobectomy plus radiation therapy with an average tumor dose of 5,638 rads. The average survival time post lobectomy was 22.3 months and 14.8 months post irradiation (Table VIII).

The results indicate a slightly better

TABLE VI SURVIVAL OF PATIENTS (FEMALE) WITH LUNG CARCINOMA (May 1955-June 30, 1964)

No. of Patients	Irradiation Only	Tumor Dose (Co ⁵⁰) 4,5∞ rads+	Survival* (mo.)
Living Deceased	18	4,504 5,270	5 10.3
Total	19.	5,230	10.0

less than 4,500 rads tumor dose

Living	1	4,496	1.∞
Deceased	12	2,644	4.50
Total	13	2,786	4.2

^{*} Survival calculated from last day of first treatment series.

[†] Survival calculated from last day of first treatment

[†] Survival calculated from last day of first treatment series.

Table VII

SURVIVAL OF PATIENTS (MALE) FOLLOWING
PNEUMONECTOMY AND IRRADIATION
(May 1955–June 30, 1964)

	Pneumo-	Tumor	Surviva	ıl (mo.)
No. of Patients	nectomy and Irradia- tion	Dose (Co^{60}) 4,5 ∞ rads+	Post Surgery*	Post Irradia- tion†
Living	9	5,064	36.3	30.5
Deceased	33	5,639	12.9	9.5
Total	42	5,516	17.9	14.0
	same cate ∞ rads tun		with less	
Living	2	4,374	6. ı	5.6
Deceased	9	2,817	8.0	4.4
Total	11	3,100	7.6	4.6

^{*} Survival calculated from day of surgery.

survival for the patients who had lobectomy plus radiation therapy. Also, the immediate surgical mortality was lower for the lobectomy patients.

TABLE VIII

SURVIVAL OF PATIENTS (MALE) FOLLOWING
LOBECTOMY AND IRRADIATION

(May 1955-June 30, 1964)

	Lobec-	Tumor	Surviva	l (mo.)
No. of Patients	tomy and Irradia- tion	Dose (Co^{60}) 4,5 ∞ rads+	Post Surgery*	Post Irradia- tion†
Living Deceased	9 22	5,187 5,823	36.97 16.32	29.31 8.92
Total	31	5,638	22.31	14.84
•	s in above 1 4,500 rad		some with	1
Living	12	5,068	29.23	23.55
Deceased	33	4,929	16.39	9.13
Total	45	4,961	19.81	12.97

^{*} Survival calculated from day of surgery.

Langdon et al.⁸ reported a series of 24 patients (20 males and 4 females) who had inoperable lung carcinoma and who received a minimum tumor dose of 3,500 r to the primary lesion and mediastinal drainage areas combined with 5-FU. At least 3 gm. of 5-FU was given in divided doses. The average survival time was 4.7 months. These patients are also included in this series.

Although nitrogen mustard can produce brief dramatic results in patients with the

Table IX
SURVIVAL OF PATIENTS (MALE) FOLLOWING
THORACOTOMY, IRRADIATION AND 5-FU
(May 1955-June 30, 1964)

	Thora-	Tumor	Surviva	l (mo.)	
No. of Patients	cotomy, Irradia- tion and 5-FU	Dose (Co^{60}) 4,5 ∞ rads+	Post Surgery*	Post Irradia- tion†	
Living Deceased	I 9	5,070 4,34I	2.0 11.53	o 9.25	
Total	10	4,4 ¹ 4	10.63	8.32	
Patients as	above wit herapy but				
Living Deceased	13	5,070 5,713	2.5 8.81	o 6.12	
Total	14	5,667	8.3€	5.68	
Patients as above (chemotherapy but not 5-FU) and some with less than 4,500 rads					
Living Deceased	18 I	5,070 5,∞8	2.5 8.39	o 5.58	
Total	19	5,011	8.08	5.29	

^{*} Survival calculated from day of surgery.

[†] Survival calculated from last day of first treatment series.

[†] Survival calculated from last day of first treatment series.

[†] Survival calculated from last day of first treatment series.

Table X

SURVIVAL OF PATIENTS (MALE) FOLLOWING
LOBECTOMY, IRRADIATION AND
CHEMOTHERAPY

(May 1955-June 30, 1964)

	Lobec-	Tumor	Surviva	ıl (mo.)
No. of Patients	tomy, Irradia- tion and Chemo- therapy	Dose (Co^{60}) 4,5 ∞ rads+	Post Surgery*	Post Irradia- tion†
Living Deceased	1 5	4,680 5,285	63 23.55	3·5 13.1
Total	6	5,184	30.13	11.5
Patients as	above but	some wit	h less than	4,5∞ rads
Living Deceased	1 9	4,680 4,304	63 25.86	3·5 9·78
Total	10	4,341	29.58	9.15

^{*} Survival calculated from day of surgery.

superior vena caval syndrome, equally good results can be obtained using radiation therapy. The beneficial effects, however, may not appear as rapidly as when nitrogen mustard is used. No claims have been made that patient survival rates will be prolonged by the utilization of chemotherapy.

Sutton¹⁷ found that the 6 month survival time of 20 patients who had superior mediastinal obstruction due to carcinoma of the bronchus and who were treated with demecolcine or N-desacetyl-N-methyl-colchicine (Ciba) combined with radiation therapy increased from 26 per cent to 45 per cent.

Morrison et al. compared 2 groups of patients with clinically operable carcinoma of the bronchus. One group of 30 patients had surgery and the other group of 28 patients had supervoltage therapy. The I year survival rate was better for patients receiving radiation therapy, but at subsequent yearly intervals those who had surgery showed a higher percentage of survival. At the end of 4 years, 23 per cent

Table XI
5-fu combined with thoracotomy and irradiation (males)

	C 40	Surviv	al (mo.)		
No. of Patients	Co ⁸⁰ 3,∞0 rads+	Post Thora- cotomy	Post Irradiation		
Living 0 Deceased 11	4,520	10.5	8.1		
5-FU COMB	NED WITH I	RRADIATION	(MALES)		
No. of Patients	Co ⁶⁰ 3,∞∞ rads+	Survival (mo.)			
Living 0 Deceased 19	4,810	5.0			
5-fu combined with lobectomy and irradiation (males)					
No. of	Co60	Surviv	al (mo.)		

Nf		Co ⁶⁰	Survival (mo.)		
	No. of Patients		Post Surgery	Post Irradiation	
Living Deceased	o 4	4,863	² 4·3	13.2	
	-			,	

5-FU COMBINED WITH IRRADIATION (FEMALES)

No. of Patients		C_0^{60} 3, ∞ 0 rads $+$	Survival (mo.)	
Living	0			
Deceased	7	4,322	5.4	

of the surgical group survived and only 7 per cent of the radiation therapy group. The results of treatment according to histologic cell type are shown below.

	Squa- mous Cell Carci- noma	Four Year Survi- vors	Ana- plastic Cell Carcinoma	Four Year Survi- vors
Radiation therapy Surgery	17 20	1 (6%) 6 (30%)	9 10	1

[†] Survival calculated from last day of first treatment series.

Table XII

SURVIVAL (MALES) RECEIVING COMBINED
THERAPY FOR LUNG CARCINOMA
(May 1955-June 30, 1964)

No. of Patients		Tumor Dose 3,500 rads+	Survival (mo.)
Living	0		
Deceased	23	4,214	4.5
	Lobectomy, Irradiation and 5-FU		
Living	0		
Deceased	4	4,863	13.2
Р	neumonectom Irradiation and 5-FU	у,	
Living	0		
Deceased	I	3,∞∞	17.7

Shanks¹⁴ reported the results of radiation therapy in lung cancer as follows: "Windeyer (quoted by Buschke in 1957) reported 4 cases of 6-year survival in over 200 cases treated and Smithers (1953) 6 cases of 5-year survival in over 171 cases radically treated. Hilton (1955) recorded 8 cases of 5-year survival in a series of 203 cases, and Dobbie (1944) 2 cases of 5-year survival in 170 treated cases." Shanks also

Table XIII

SURVIVAL OF PATIENTS (MALE) FOLLOWING
PNEUMONECTOMY, IRRADIATION AND
CHEMOTHERAPY

(May 1955-June 30, 1964)

No of	Pneumo- nectomy, Irradiation	Tumor Dose		vival 10.)
Patients	and Chemo- therapy	(Co ⁶⁰ or 6 mev.)	Post Sur- gery*	Post Irradia- tion†
Living Deceased	o 6	Average 4,924 rads	16.08	9/58

^{*} Survival calculated from day of surgery.

TABLE XIV

SURVIVAL OF PATIENTS (FEMALE) FOLLOWING
LOBECTOMY ONLY AND LOBECTOMY
AND IRRADIATION

(May 1955-June 30, 1964)

No. of Patients	Lobec- tomy Only	Survival (mo.)		
Living	2	46.9		
Deceased	4	11.4		
Total	6	23.20		
	Lobec-	Tumor	Surviva	ıl (mo.)
	tomy and	Dose - (Co ⁸⁰)		Post
	Irradia-	4,5∞	Post	Irradia-
	tion	rads+	Surgery	tion
Living	2	5,061	17.6	15.6
Deceased	3	5,630	20.0	8.3
Total	5	5,402	19.1	11.3
	Lobec-	Tumor		
	tomy	Dose		
	and	Less Than		
	Irradia-	4,5∞		
	tion	rads		
Living	0		ala da da da da da sa sa sa sa gantana ngabar	
Deceased	I	2,978	10.7	9.5

Table XV

SURVIVAL OF PATIENTS (FEMALE) FOLLOWING

IRRADIATION AND CHEMOTHERAPY

(May 1955-June 30, 1964)

No. of Patients	Irradiation and Chemotherapy	Tumor Dose (Co ⁶⁰) 4,5∞ rads+	Survival* (mo.)		
Living	I	5,125	0		
Deceased	5	5,673	4.6		
Total	6	5,582	3.83		
All patients as in above category but some with less than 4,500 rads					
Living	2	4,285	8.88		
Deceased	13	3,759	4.6		
Total	15	3,829	5.17		

^{*} Survival calculated from the last day of the first treatment series.

[†] Survival calculated from last day of first treatment series of over 4,500 rads tumor dose.

TABLE XVI SURVIVAL OF PATIENTS (FEMALE) FOLLOWING PNEUMONECTOMY AND IRRADIATION (May 1955-June 30, 1964)

	Pneumo-	Tumor	Surviva	al (mo.)
No. of Patients	nectomy and Irradia- tion	Dose (Co^{80}) 4,5 ∞ rads+	Post Surgery	Post Irradia- tion
Living	1	5,183	I	1.75
Deceased	2	5,517	3.75	1.75
Total	3	5,406	3.83	1.78
	ts as in about			some wh
Living	1	5,183	4.00	1.75
Deceased	6	3,830	7.79	2.29
Total	7	4,023	7.25	2.50

cited 2 patients out of 126 patients (1.5 per cent) living for 5 years who were treated by roentgen-ray therapy alone (4,000 r in 4 Schulz,18 using megavoltage therapy, obtained an average survival time of 8 months in 232 patients with inoperable lung cancer. Three of his patients survived for more than 5 years.

TABLE XVII SURVIVAL OF PATIENTS (FEMALE) FOLLOWING LOBECTOMY AND IRRADIATION (May 1955-June 30, 1964)

-	Lobec-	Tumor Dose	Surviva	l (mo.)
No. of Patients	tomy and Irradia- tion	(Co ⁶⁰) 4,500 rads+	Post Surgery*	Post Irradia- tion†
Living	2	5,061	17.8	15.6
Deceased	3	5,633	20.0	8.33
Total	5	5,403	19.05	11.25
	s as in abo		ry but som	e with
Living	2	5,061	17.8	15.6
Deceased	4	4,967	17.69	8.62
Total	6	4,999	17.5	10.97

TABLE XVIII

SURVIVAL OF PATIENTS (FEMALE) FOLLOWING THORACOTOMY, IRRADIATION AND CHEMOTHERAPY

(May 1955-June 30, 1964)

NT C	Thora- cotomy,	Tumor Dose	Surviva	l (mo.)
No. of Patients	Irradia- tion and Chemo- therapy	(Co ⁸⁰) 4,500 rads+	Post Surgery*	Post Irradia- tion†
Living Deceased	o 3	6,104	12.25	9.92

^{*} Survival calculated from last day of first treatment series. † Survival calculated from day of surgery.

Guttmann⁶ reported a 5 year survival time of 7.4 per cent in a group of patients where the inoperability became evident only after thoracotomy. A tumor dose of 5,000 rads was delivered in 5 weeks through large opposing fields, including the mediastinum. She used 2 million volt therapy equipment with a half value layer of 7 mm. of lead and a target skin distance of 100

There were 19 patients in the UCLA series who lived over 4 years after diagnosis and treatment. Four males had pneumonectomy and have survived from 57.4 to 140 months; 2 male patients had pneumonectomy plus postoperative radiation therapy with a survival time from 83 to 85 months; 2 had lobectomy only and are living from 86 to 98 months; 5 had lobectomy plus radiation therapy with survival

TABLE XIX SURVIVAL OF PATIENTS (FEMALE) WITH LUNG CARCINOMA FOLLOWING SURGERY ONLY (May 1955-June 30, 1964)

No. of Patients		Lobec- tomy	Pneumo- nectomy	
Living	0	2 (1 alve- olar cell)	0	43.87
Deceased	r	4	0	11.38
Total	r	6	0	22.21

^{*} Survival calculated from day of surgery.

^{*} Survival calculated from day of surgery. † Survival calculated from the last day of first treatment series.

Table XX

SURVIVAL OF PATIENTS (MALE) WITH LUNG
CARCINOMA FOLLOWING SURGERY ONLY
(May 1955-June 30, 1964)

No. of Patients	Thora- cotomy	Lobec- tomy	Pneumo- nectomy	Survival (mo.)*
Living	I	6	5	24.0 48.0 82.1
Deceased	13	12	10	5.21 14.0 10.3
Total Average	14	18	15	
Survival	6.55	25.4	34.2	

^{*} Survival calculated from day of surgery.

time from 50.75 to 65 months. There were 4 males treated by radiation therapy only (I had thoracotomy for diagnosis) with a survival time from 56 to 87 months. Only 2 females have survived over 4.5 years. One was treated by lobectomy only and I had radiation therapy only. Both of these patients had primary adenocarcinoma of the lung. Five of the 19 long term survivors (25 per cent) had radiation therapy only and 50 per cent of the remaining 14 patients had surgery combined with postoperative radiation therapy.

Bloedorn et al.¹ believe that radical radiation therapy together with radical surgery is feasible in many patients with bronchogenic carcinoma and that the primary tumor can be sterilized in a high percentage of cases. Their preliminary studies have shown promise. This method of combined therapy is under investigation in a number of clinical centers and an excellent evaluation of this method of therapy should soon be forthcoming.

The survival data for patients treated by surgical procedures only are shown in Tables XIX and XX.

SUMMARY

The average survival of 620 deceased males with lung cancer irrespective of type

of treatment was 7.39 months, of the deceased female patients, 6.89 months. The survival time was calculated from the day of surgery or from the last day of the first treatment series. Eighty-two per cent of the males and 80.4 per cent of the females died during the first year.

Although attempts have been made to predict the rate of growth of malignant tumors, considerable variation exists in the rate of growth of primary lung carcinomas in individual patients.

On the basis of the survival data of untreated lung cancer patients (average survival time of approximately 3.5 months), radiation therapy should be recommended to patients with lung cancer because of the improvement in survival time and the palliative effect on the patient following its use.

Roentgenographic findings of lung cancer may be present long before the patient has any clinical symptoms. The development of a high index of suspicion for lung cancer in all physicians participating in the diagnosis of chest diseases should be encouraged.

It is possible to cure a small percentage of patients with lung cancer by radiation therapy; a higher percentage of patients with operable lesions are cured by surgery used either singly or in combination with radiation therapy.

Excellent palliation is obtained in approximately 65 per cent of the patients following the use of radiation therapy. The use of chemotherapeutic agents has little clinical value in lung cancer therapy.

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AN EVALUATION OF THE RADIOTHERAPEUTIC MANAGEMENT OF INTRACRANIAL GLIAL TUMORS WITHOUT PRIOR SURGERY*

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THE usual methods of treating the more malignant intracranial glial tumors are partial resection, partial resection followed by radiotherapy, and biopsy followed by radiotherapy. Reported series^{1,4,7,8,9,10,14} indicate that partial resection followed by radiotherapy results in a longer survival time than either partial resection alone or biopsy followed by radiotherapy. The results of a less usual method of treatment of these lesions, radiotherapy alone, will be evaluated.

MATERIAL

Table I shows the total number of patients who were treated for intracranial tumors in the Radiotherapy Department of the Mount Sinai Hospital, New York, from January I, 1960 to December 31, 1963. This table does not include those patients registered in the Hospital with the diagnosis of intracranial tumors who did not receive radiotherapy.

In the group of metastatic tumors (134), the number of patients presenting with intracranial disease following a previously proven primary lesion far exceeded that number in which the intracranial manifestation was the first evidence of disease. Patients who had a previous craniotomy (62) are not considered. Pineal and pituitary tumors, as well as lesions of the brain stem and posterior fossa associated with a better prognosis (72) are not included in this evaluation. This leaves a total of 77 patients referred with a diagnosis of malignant intracranial glioma made on clinical, neuroradiologic, radioisotope scanning and electroencephalographic findings, who were accepted for radiotherapy without prior craniotomy.

Table I
INTRACRANIAL TUMORS TREATED 1960-1963

Metastatic Tumors	134
Primary Tumors Surgery+Radiation	62
Radiation Only Excluded 72 Assessed 77	149
Total	345

METHOD OF TREATMENT

All patients in this series were treated on a cobalt 60 unit at a treating distance of 50 cm. The stated doses are those calculated from isodose curves derived from direct measurements made in a pressdwood phantom. These doses can be expected to vary only insignificantly due to absorption in the calvarium.⁸

The over-all treatment time in the majority of patients was 5 weeks. In those instances where this was not so, an equivalent 5 week dose was estimated.12 Patients who were acutely ill or who had evidence of raised intracranial pressure at the beginning of treatment were started on low daily doses which were gradually increased -a so-called crescendo technique-until an even input rate could be given. If, in spite of low dosage, the patient's condition continued to deteriorate, corticosteroids were given. Different dose levels were used in a sequential manner to estimate whether varied doses would influence progress of the disease.

RESULTS OF TREATMENT

Radiation seldom, if ever, eradicates

^{*} Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8-10, 1965.

glioblastoma multiforme. The prime purpose in treating these patients is to attain maximal return of function. A critical analysis of the degree of palliation, however, presents many problems and seldom affords valid comparison with other series. For this reason, the survival time only will be considered.

Table II shows the survival time in months of the 77 patients assessed. The 4 patients lost to follow-up completed the course of treatment but no further information could be obtained after their discharge from hospital. For purposes of assessment, these patients are assumed to have died within 3 months of treatment.

Of the 77 patients assessed, 24 survived more than 1 year (31 per cent). If, however, the 12 patients who died within the first month of treatment, not having completed the prescribed course of therapy, are excluded, the survival rate is 24/65; *i.e.*,

TABLE II
SURVIVAL TIME IN MONTHS

Less than I month	12
More than I and less than 3 months	11
More than 3 and less than 6 months	11
More than 6 and less than 9 months	10
More than 9 and less than 12 months	5
More than 12 months	24
Untraced	4
	Made Invoke
	77

37 per cent (Fig. 1). This compares favorably with the results of partial resection followed by radiotherapy in published series^{1,7,14} (Fig. 2), where those patients who died within the first month are similarly excluded.

It was of interest to determine whether unrelieved intracranial pressure contributed to the early death of those patients

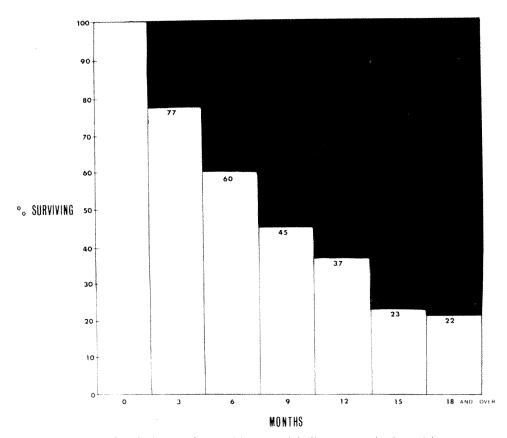


Fig. 1. Survival rate of treated intracranial glioma cases (1960-1963)

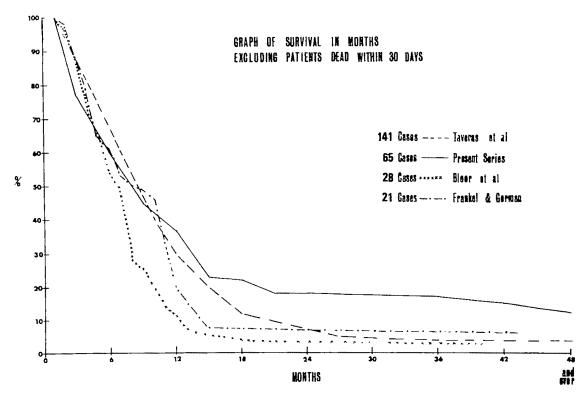


Fig. 2. Survival curves of patients treated with radiotherapy following partial resection in 3 different series are compared with patients treated with radiotherapy alone in the present series.

not completing the prescribed course of radiotherapy. In only 2 of these patients was raised intracranial pressure found prior to their demise. In both cases, the lesion was extensive and "deep" and in 1 patient, it was on the dominant side.

Table III shows the subsequent survival rate of patients who did not die within the

Table III

PATIENTS SURVIVING MORE THAN 12 MONTHS

	Known Dead	Still Alive
Less than 15 months	9	0
Less than 18 months	ī	2
Less than 21 months	2	5
Less than 24 months	0	ō
Less than 36 months	1	I
Less than 3.5 years	1	I
More than 5 years	0	I
	14	10

first year of treatment. Of those still alive, 10 have survived 18 months; 4 have survived 2 years; 2 have survived 3 years and 1 has survived 5 years.

In previously reported series, there are conflicting opinions as to the influence of age on survival. In this group of patients (Table IV), it would appear that those patients under 39 did have a better survival rate.

There is no significant difference in the survival rate in the equivalent tumor dose

Table IV

ONE YEAR SURVIVAL RELATED TO PATIENT'S AGE

Years	Survival	
20-39	5/6 2/8	
40-49	2/8	
50-59	13/25	
60-69	3/27	
70-79	1/11	

Table V

ONE YEAR SURVIVAL RELATED TO
EQUIVALENT 5 WEEK DOSE

Dose	Survival
4,000 rads	3/5
4,500 rads	3/8
5,∞0 rads	5/18
5,500 rads	9/18
6,000 rads	0/4
6,500 rads	3/8
7,∞∞ rads	1/2

range of 4,000-7,000 rads given in 5 weeks (Table v). As an initial assessment of survival time done after the third year, did not indicate an advantage in increasing the dose above 5,500 rads in 5 weeks, and the reactions at higher dose levels were moderately severe, the greater number of patients received a tumor dose between 5,000 and 5,500 rads. Although this dose is higher than the usually accepted tolerance levels,2,11 in view of the poor prognosis in this group of patients and variance of opinion as to tolerable levels,4 these doses were considered justified.

The two most commonly used techniques were either a parallel opposed pair of fields (10×10 or 10×14 cm.) or a 4 field beam directed technique, biased towards the sides of the lesion utilizing two 10×10 cm. fields, in the anteroposterior axis and two 10×14 cm. fields in the lateral axis. As expected, the treatment technique had no significant influence on the survival rate (Table vi). The 4 field beam directed technique, however, had the advantage of preserving the hair on one side of the head. Except in the acutely ill patient, the head was usually shaved to avoid maximum build up on the scalp and to facilitate ac-

Table VI

ONE YEAR SURVIVAL RELATED TO
TREATMENT TECHNIQUE

Four field beam directed	14/33 10/30	
--------------------------	----------------	--

Table VII

ONE YEAR SURVIVAL RELATED TO FIELD SIZE

Field	Survival
ıo×10 cm.	14/29
10×14 cm.	14/29 10/32

curate alignment of fields at each treatment session. The eyes were shielded on the lateral field and the anteroposterior fields were slightly tilted to avoid the eyes (Fig. 3).

The infiltrating nature of these lesions¹³ and the disparity between the size of the lesion as seen on neuroradiologic studies and the actual size as demonstrated at postmortem examination⁵ were appreciated at the beginning of the series. Field sizes of less than 10×10 cm. were not used. Subsequent publications^{6,15} have accentuated the advisability of avoiding small fields in treating these lesions. Whether 10×10 or 10×14 cm. fields were used did not influence the survival rate (Table VII).

CORRELATION OF HISTOLOGY WITH CLINICAL DIAGNOSIS

Of the 77 patients assessed, 63 patients were known to be dead, 10 were still alive at the time of assessment, and 4 remained untraced. Forty-nine patients died within the first year (Table VIII) and 14 died after having survived 12 months (Table IX). Except in 2 cases, the histology was obtained at postmortem examination. In these 2 exceptions, the histology was obtained at the time of subsequent operation at other hospitals.

In only 3 of the 29 patients where the diagnosis was verified was the histology other than that of malignant glial tumor. These patients deserve special mention. Both of the patients who proved to have metastatic lesions were treated as presumptive glial tumor cases after investigation failed to reveal a primary focus of disease. Both were dead within 4 months of treatment with widely metastatic lesions. The patient who subsequently proved at postmortem examination to have an intra-

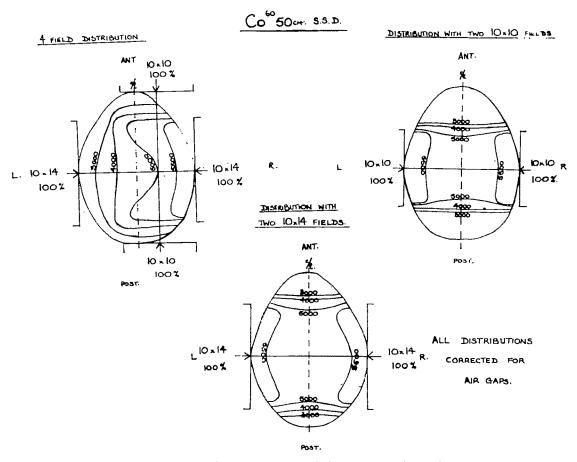


Fig. 3. Isodose distribution with the techniques commonly employed.

ventricular meningioma was a 67 year old female, admitted with left hemiparesis, severe arteriosclerotic heart disease and auricular fibrillation. Angiography showed a stippled tumor deep in the right posterotemporal lobe. The patient's condition deteriorated rapidly in the absence of evidence of raised intracranial pressure and she died after only 2 treatment sessions of a massive pulmonary embolus.

DISCUSSION

On assessing the reported results of the treatment of the more malignant intracranial glial tumors, it is apparent that although partial excision does give increased survival time over biopsy only, it is only when partial excision is followed by postoperative radiotherapy that the survival time is significantly increased (Fig. 4). A similar increase in the survival time is

Table VIII
HISTOLOGY ON PATIENTS KNOWN DEAD WITHIN I YEAR

Histology not obtained	26		
Histology obtained	23		
- -	-	Glioblastoma	16
		Astroblastoma	I
		Astrocytoma Grade 11-111	3
		Ventricular meningioma	ī
		Metastatic lesions	2

Table IX
HISTOLOGY ON PATIENTS KNOWN DEAD SURVIVING MORE THAN 1 YEAR

Histology not obtained	8		
Histology obtained	6		
		Glioblastoma	5
		Astroblastoma	ĭ

noted in those patients who have biopsy only followed by radiotherapy. It was concluded, therefore, that the increase in survival time in these patients was mainly due to the radiotherapy.

The above conclusion, in conjunction with the increased accuracy in diagnosing these lesions, prompted the decision to treat patients diagnosed as having malignant intracranial gliomata without prior craniotomy. This would obviate post-operative mortality and morbidity and afford information as to the value of radiotherapy when used as the sole effective therapeutic agent in these tumors.

This treatment approach can be justifiably criticized on the basis that if even in the occasional case the diagnosis is in error, the chance of cure may be lost and the patient be subjected to doses of radiation which may result in postradiation brain injury. In analyzing this group of patients, in the 3 instances in which an error of diagnosis was made, surgery would not have benefitted 2 of the patients with metastatic disease, and it is extremely doubtful whether surgery would have altered the outcome in the third with an intraventricular meningioma. It is interesting to note that in those patients who survived a year, with a postmortem rate similar to those patients who died within I year, the histology verified the clinical diagnosis without exception.

Considering the patients who did survive a longer period, it would appear that this increase in survival rate was appreciably better than would be expected in patients with a histologic diagnosis of malignant glioma, and that possibly these patients have, in fact, more benign lesions.

This may, of course, be the case and later evaluation will clarify this. It must be pointed out, however, that the results in Figure 2, with the exception of the results of Bloor et al., were obtained with doses both above and below 4,000 rads. If the present series is compared with groups of patients receiving doses in the same range, where this information is available (Fig. 3), the results are similar. The occasional long term survivor, in patients treated with partial excision followed by radiotherapy—pathologically proven—is not unusual, and the fact that 2 patients in this group have

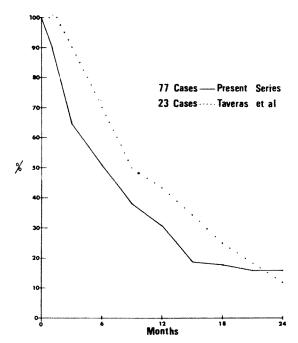


Fig. 4. Over-all survival curves of patients having received more than 4,000 rads. The present series was treated without prior craniotomy, the series of Taveras *et al.* after partial excision. Exclusion is not made of those patients dying within the first month of treatment.

survived 3½ years does not necessarily indicate that there was an error in the initial diagnosis.

It must be stressed that this method of treatment was undertaken because of the complete confidence in the accuracy of the clinical diagnosis and is not advocated in any other circumstances. Where doubt exists, it is essential that histologic verification be obtained before treatment is given.

SUMMARY

A group of 77 patients, clinically diagnosed as having the more malignant glial tumors in which radiotherapy was the sole effective therapeutic agent, is evaluated. If the 12 patients who died within the first month and, therefore, did not complete the proposed course of therapy are excluded, the 1 year survival rate (24/65; 37 per cent) compares favorably with published results of patients treated with radiotherapy following partial excision.

Treatment volumes in excess of 1,000 cc., or tumor doses above 4,000 rads in 5 weeks, did not alter the prognosis. Postmortem histology obtained in 46 per cent of the cases confirmed the clinical diagnosis in all but 3 instances in those patients who lived less than 12 months, and in all those patients who survived more than 1 year.

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EFFECT OF A STAINLESS STEEL MESH SKULL PROSTHESIS ON THE DEPTH DOSE DISTRIBUTION OF 200 kv. ROENTGEN RAYS, CO⁶⁰, AND HIGH ENERGY ELECTRON BEAMS

A PRELIMINARY STUDY ON BRAIN IRRADIATION AFTER STEEL MESH CRANIOPLASTY

By G. P. TOSI,* F. COLUMELLA,† G. B. DELZANNO,† G. GAIST,† and G. PIAZZA† MILANO AND BOLOGNA, ITALY

THE satisfactory results obtained with stainless steel mesh in 59 cranio-plasties (Fig. 1)¹ stimulated the present study, which was conducted in order to evaluate the possible interference of this type of prosthesis with postoperative radiation therapy. A comparative analysis was made of the dose distribution in depth, when the head is exposed to the beam of high energy (32 mev.) electrons from a betatron, to the gamma radiation of a Co⁶⁰ unit, and to 200 kv. conventional roentgen rays, respectively.

A special study was conducted on the modifications of the absorption curves when bone defects in the skull vault are repaired with stainless steel mesh. Under these conditions, the beam of ionizing radiations traverses a nonhomogeneous structure, with areas of high density, capable of absorbing part of the beam and of producing a considerable amount of secondary radiation.

METHOD

A mock "head", or phantom (Fig. 2), was made from a block of masonite of a density equivalent to that of the soft tissues. Upon this a 14×14 cm. $(5\frac{1}{2}\times5\frac{1}{2}$ inch) square of stainless steel mesh was applied which previously had been immersed in a 50 per cent paraffin-wax mixture, in order to fill the spaces with a substance having a density equal to that of the soft structures.

For photodensitometric measurements,

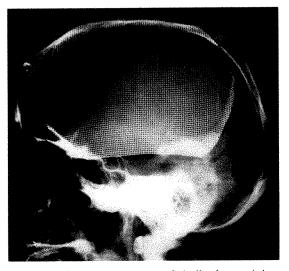


Fig. 1. Plain roentgenogram of skull after stainless steel mesh cranioplasty.

the core of the masonite phantom, along the direction of the radiation beam, was fitted with an X-ray film, one edge of which was in contact with the steel mesh. Eastman Kodak Industrial M-type film, which is suitable for exposure to high energy radiation because of its high definition, low sensitivity, and good quality for reproduction, was used.

The phantom was then exposed, through an 8×10 cm. ($3\frac{1}{8} \times 4$ inch) port to a low (8 r) dosage in order to produce on the film a darkening corresponding to the linear segment of the sensitivity curve (density $1 \div 1.5$). The darkened areas were measured with a Hilger microphotometer, using

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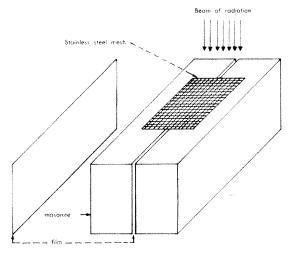


Fig. 2. Masonite mock "head" covered by stainless steel mesh and containing strip of X-ray film.

a slit opening with sides of 10 μ and 70 μ , respectively, with a ratio 1:7.

The microphotometer was connected to a pen recorder, and a direct tracing of the curves was thus obtained. Measurements were also taken of various darkened areas on the film in order to consider the possible associated presence of scattered radiation, and to eliminate the variations due to the developing and fixing processes.

Control of the photodensitometric data was obtained by ionimetric analysis of the absorption curves. Ionization chambers, sensitive to high-energy electrons and to X and gamma rays, having tissue-equivalent walls of 6 mm. (outside diameter) and an internal volume reduced to the point of not causing appreciable changes of the depth dose distribution, were used. The response of these chambers, linear with the dose, was measured with an integrating dosimeter, Duplex PTW type. The chambers were introduced into cavities of the masonite block and placed at distances which would permit measurements every 4 mm. in depth. The maximum possible error of measurement of these chambers, which had previously been gauged against a standard source of radium element of known intensity, is in the order of ∓ 6 per cent. Within these limits, the results obtained with these chambers fully corresponded to those obtained with the photodensitometric method.

RESULTS

I. IRRADIATION WITH 32 MEV. ELECTRON BEAMS FROM A BROWN-BOVERI BETATRON

Irradiation with 32 mev. electron beams from a Brown-Boveri betatron resulted in the absorption curves shown in Figure 3. Curve 1, which can be used as a reference, represents the depth dose after the beam had passed through structures corresponding to the soft tissues. Curve 2 shows the depth distribution when the skull was irradiated from an external source. The presence of the bone, the density of which, while higher than that of the soft tissues is not high enough to produce an appreciable amount of secondary radiation, causes a diminution of 6-7 per cent in the dose absorbed in depth. Curve 3 refers to the electron beam after it had traversed the stainless steel mesh. This mesh has a density of 7.93 gm./cm.3, and is therefore capable of an appreciable screening effect on the electron beam.

The peak of the absorption curve (which had been calculated as a mean of the curves corresponding to the screen interstices and to its solid components, respectively) is dis-

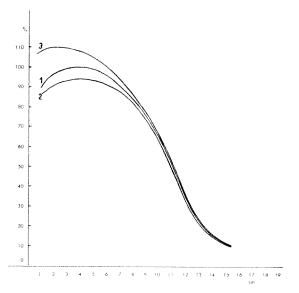


Fig. 3. Absorption curves of 32 mev. electron beams: 1—in soft tissues; 2—past bone; and 3—past stainless steel mesh.

placed I-I.5 cm. toward the surface because of secondary low-energy, nonpenetrating radiation caused by the interaction of the electrons with the steel of the mesh. The presence of such secondary radiation accounts for the percentile increase in the dose absorbed in the first few centimeters. Deeper within the block, the low-energy secondary radiation is extinguished, and the difference between Curve 2 and Curve 3, which is greatest at I cm. (where it reaches 15-20 per cent) decreases until at 7-8 cm. the two curves approximate each other. The approximation is so close that the two curves can practically be considered as superimposed. This is due to the fact that the margin of error is in the order of \pm 6 per cent, and the distance between the two curves is less than this value. Figure 4 shows the radiation pattern transmitted by the steel screen at a depth of 2 mm. To obtain it, the film was read along a straight line parallel to its edge and 2 mm. from it. The minimal dose areas (indicated by 90 per cent) correspond to the solid screen; areas indicated by 100 per cent correspond to the interstices, while the peaks of 110 per cent represent the side-scattering effects along the woven edge of the mesh. This lack of uniformity in the beam's cross section decreases very quickly, and at 2-2.5 cm. the beam is again uniform.

II. IRRADIATION WITH GAMMA RAYS OF 1.173 AND 1.332 MEV. FROM A SOURCE OF CO⁶⁰

The measurements have shown that the presence of the steel mesh does not cause

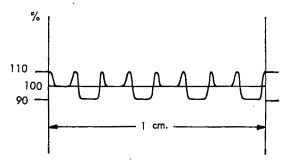


Fig. 4. Radiation pattern transmitted by stainless steel mesh at a depth of 2 mm. (electron beam irradiation).

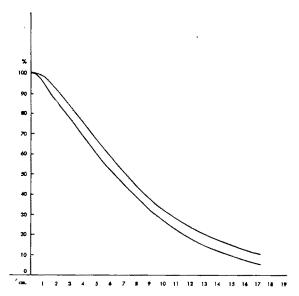


Fig. 5. Absorption curves of conventional X-rays (200 kv.): upper curve—in soft tissues and lower curve—past stainless steel mesh.

appreciable changes in the depth dose distribution. The increase in the first few millimeters of the absorbed dose, due to scattered and characteristic radiations, is compensated by the decrease (however small) due to the absorption in the solid components of the mesh. Within the limits of precision of the types of measurements used (\pm 6 per cent), the integral absorbed dose was the same, with or without steel mesh, and the corresponding transmission curve in depth was practically unaltered. The lack of uniformity of the beam's cross section is in the order of 2-3 per cent, and does not cause any appreciable modification in the isodoses in depth.

III. IRRADIATION WITH CONVENTIONAL X-RAYS (200 KV., I MM. CU)

Figure 5 shows the absorption curves of the X-ray beam which was employed. The upper curve represents the dose absorbed in depth after the beam had gone through structures of density equal to that of the soft tissues of the irradiated region. The lower curve refers to the X-ray beam after traversing the stainless steel mesh. It can be observed that the absorbed dose is the

same only on the surface, where the scattered and characteristic radiations of the mesh metal of low penetration compensate for the lack of intensity due to the passing of the beam through the mesh's solid structure. In depth, on the other hand, the absorbed dose in the presence of the mesh is about 7 per cent lower than the dose absorbed under normal anatomic conditions. The cross section of the beam repeats in depth for about 10 cm. the pattern of the mesh, having an absorption which is about 15 per cent lower in areas corresponding to its interstices. The average effect is a difference of about 7-10 per cent from the dose absorbed without the mesh.

SUMMARY AND CONCLUSIONS

The present investigation concerns the modifications induced on the irradiation depth dosage by stainless steel mesh (as used for cranioplasties), when the mesh is interposed on the radiation beam (32 mev., Co60, 200 kv. X-rays).

The study was conducted in order to assess which type of radiation therapy is to be preferred after stainless steel mesh cranioplasty.

The mesh was found to have a considerable screening effect on 200 kv. X-rays and, also, to cause a modification in their homogeneity.

A minimal screening effect was observed on 32 mev. electron beams, and their homogeneity was modified by the mesh only for 1.5-2 cm.

The presence of the mesh induced practically no modifications on Co60 radiation

It is, therefore, the conclusion of the authors that whenever radiation therapy of the brain is to be used on patients with stainless steel mesh crainoplasty, electron beam or Co60 radiations are to be preferred over conventional X-rays.

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COMBINED RADIATION AND REGIONAL CHEMOTHERAPY IN THE TREATMENT OF RETINOBLASTOMA*

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THE concept of treatment of retinoblastoma has been in a state of change in the past decade due to the advances in irradiation techniques and chemotherapy. The once rather dismal prospect of treatment with unilateral or bilateral enucleation, or with the heavy dose of irradiation necessary for cure but with a high incidence of side effects such as retinal damage, cataract formation, injury to the soft tissue of the face or bones about the orbit, or even late sarcomatous changes, has been largely replaced. 4.6,12,17

In 1952, Kupfer⁹ combined the use of systemic nitrogen mustard with radiation in the treatment of a child with recurrent retinoblastoma, obtaining good results. In 1953, Reese and associates18 combined the use of oral triethylenemelamine (TEM) with lower doses of radiation and were able to report a better salvage rate with fewer complications. In cases of poor prognosis, i.e., patients with nerve or orbit involvement or with bilateral disease, a single dose of TEM was administered through the internal carotid artery and followed by fractional irradiation with improved results.14 In 1958, we introduced the use of fractional intra-arterial TEM combined with irradiation for cases of poor prognosis and have found the method of value. 7,8 This paper deals with the indications and the techniques that we are presently using and the results of this type of therapy.

TREATMENT INDICATIONS

The indications for treatment of retinoblastoma by fractional intra-arterial chemotherapy and irradiation have changed with the accumulation of experience with the method. Originally, patients selected for treatment had unilateral tumor with extension into the optic nerve or orbit, or had both eyes involved. These are the cases with reduced chance of survival, and in many instances face loss of vision in both eyes. With the accumulation of experience, the indications have broadened. At this point, the primary treatment of retinoblastoma is irradiation combined with chemotherapy, provided that the diagnosis is relatively certain and that useful vision remains in one or both eyes. If irradiation fails or if there is extensive tumor resulting in severe impairment of vision, or extension of tumor into the orbit, then enucleation is indicated followed by TEM and irradiation. Thus, when the child presents with involvement of one eye with a favorable lesion and useful vision, a combination of irradiation and intravenous or intra-arterial TEM may be used. If the tumor is large and there is a good chance of extension into the optic nerve or orbit, or if residual vision is of little value, then enucleation should be carried out. If the sections show extension of tumor, the socket should be irradiated and intra-arterial TEM should be administered in an attempt to control the residual disease.

When both eyes are involved with small tumors, the combination or irradiation and intravenous or intra-arterial TEM may be used. Usually, with bilateral involvement, the child presents with one eye with advanced tumor and one eye with a small

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tumor. In this situation, the worst eye is removed, the socket is treated with irradiation, and an attempt is made to save the remaining eye with irradiation and intraarterial TEM. When the child presents with advanced tumor in both eyes, enucleation, irradiation and TEM are advised.

The use of photocoagulation⁵ and radioactive applicators¹⁶ applied directly to the globe have a place in the treatment of retinoblastoma but have not been widely adopted.

SURGICAL TECHNIQUE FOR INTERNAL CAROTID CATHETERIZATION

Internal carotid catheterization is carried out with the patient under general anesthesia and preferably at the time of operation, if enucleation is necessary. The bifurcation of the common carotid artery is exposed through an incision paralleling the anterior border of the sternocleidomastoid muscle. The common, external and internal carotid vessels are identified. The superior thyroid artery is isolated and ligated distally, and a small teflon tube (PE 50-90) is inserted into the proximal portion of the artery. The tube is then fastened in place by 2 silk ligatures tied snugly about the vessel. The artery is divided at the point of cannulization so that it can contract when the tube is removed. The external carotid artery is ligated distal to the superior thyroid artery so that drug injected into the system must enter the internal carotid artery. It is thence carried cephalad and enters the ophthalmic artery supplying the central retinal vessel and the vessels supplying the orbit in high concentration. The position of the artery can be checked by injecting I to 3 cc. of a sterile, buffered solution of fluorescein (Fluorescite) into the tube and examining the patient's eyes with a Woods light. The yellow-green fluorescence indicates the distribution of the arterial flow and, when injected into the internal carotid artery, will cause fluorescence of the eve and orbit. If the dye is injected into the external carotid artery, the face and mouth will show fluorescence.

A blunt cannula and a one-way flow valve with a two-way stopcock are inserted into the tubing. This is irrigated with a heparin-saline solution (10 mg. of heparin in 30 cc. of normal saline). Blood must not be allowed to collect in the tube, as a clot may form and block the tube. Should a clot occur, a second smaller tube may be inserted and the clot aspirated. In no instance should the clot be forced into the internal carotid system. A sterile cap is then screwed onto the stopcock to seal the system. The wound is closed in layers and the tube is sutured to the skin of the neck so that it will fall in a loop to prevent any undue traction on the tubing in the carotid artery.

The tubing, valve and stopcock are taped over the anterior chest so that they are readily available for use, yet do not inconvenience the patient. Arm splints are applied while the child is still under anesthesia, and an attendant must remain with the patient at all times. When the child has fully recovered from anesthesia and if cooperative and under supervision, the arm splints may be removed. At the completion of therapy, the intra-arterial catheter is withdrawn. If bleeding occurs, it can be controlled by point pressure over the intra-arterial wound for a 5 minute period. Nursing attendants must be instructed to apply point pressure should the tube come out inadvertently.

CHEMOTHERAPY

Triethylenemelamine (TEM) was originally produced in Germany in World War II as a cross-linking or sizing agent for the textile industry. TEM was the first of the commonly available alkylating agents that could be given by mouth and received wide usage in the past decade. It has been shown effective in the treatment of a variety of the lymphomas, chronic granulocytic leukemia¹ and in ovarian carcinomas. It is a potent inhibitor of the bone marrow and its administration has to be carefully controlled. The original dose used in this study was 0.03 mg./kg. body weight in 2 to 5 ml. of normal saline solu-

tion, given on 4 separate occasions during the course of the radiation therapy. We now find it most convenient to administer the same dose of drug immediately prior to the irradiation of the patient, with him in position on the therapy table. The present dose schedule calls for repetition of the dose of the drug up to 10 occasions, providing that the blood cell count remains adequate. Blood cell counts are obtained every other day during the course of therapy and the drug is discontinued if the white blood cell count falls below 2,500 cells per cubic mm. or if the platelets fall below 100,000 per cubic mm.

It is advisable to check the position of the catheter by the administration of fluorescein periodically during the course of treatment to ensure that the drug is entering the internal carotid artery. After the drug is administered, the tubing is flushed out with the heparin-saline solution and the sterile cap is re-applied.

RADIATION THERAPY

For the treatment of unilateral disease with the eye in place, radiation is given through a carefully-positioned 5×5 cm. retrolenticular temporal port. This is administered at 250 kv. with a half value layer of 3 mm. of copper and a focal skin distance of 50 cm. Ten treatments are given over a 2 week period with a total air dose of 3,100 r and a tumor dose of 2,500 rads. If the eye has been removed, the socket is treated using 5×5 cm. anterior and lateral ports. The therapy is fractionated over 10 treatments (total time—2 weeks) with an air dose of approximately 2,400 r per field and tumor dose of 3,960 rads.

Where it is possible to secure the cooperation of the older children, aided by sandbags and with the pupil fixed, therapy can be given without anesthesia. In younger children, radiation therapy is carried out under rectal Brevital anesthesia. The treatment is administered in the early morning and the children react sufficiently so that they may resume a normal diet by noon.

RETREATMENT

For the situation where retreatment is necessary for recurrent tumor in a remaining eye, 200 r in air is administered through a 5×5 cm. direct anterior port on 5 separate occasions. A calculated risk of cataract formation must be accepted in this situation. With recurrent tumor, direct cannulization of the common carotid artery has been carried out with a small teflon tube held in place by a purse string suture of arterial silk or through the stump of the external carotid artery if this can be easily exposed. TEM (0.03 mg./kg. body weight) is again administered on 10 occasions, providing the bone marrow is adequate and the blood cell count remains stable.

CLINICAL MATERIAL

Nineteen cases have been admitted to this study from July, 1958 through September, 1964. The patients have been treated at Charity Hospital or the Eye, Ear, Nose and Throat Hospital in New Orleans, with one exception who was treated at Hôtel Dieu.

The youngest child was 3 months of age and the oldest child was 7 years. The average age was approximately 2 years and 4 months. There were 12 males and 7 females, 14 whites and 5 Negroes. Two patients were sisters, both with bilateral involvement. Four of the children were known to have parents with retinoblastoma. Ten children had involvement of both eyes. Of this bilateral group, all came to enucleation of I eye. An attempt was made to save both eyes in the last patient with bilateral disease; however, the tumor recurred in the worst eye and despite retreatment, the eye had to be removed. Seven patients had I eye involved with histologic proof of nerve or orbit involvement. One of the patients with bilateral involvement was known to have nerve or orbit involvement in the removed eye. The last 2 patients had disease apparently confined to I eye without evidence of extraocular extension.

Five children have been retreated. Our

first patient was retreated approximately 6 months after the original therapy as the tumor had not shown satisfactory regression. Subsequent to this second course of treatment, the response has been satisfactory and the boy has 20/30 vision in his right eye; however, early cataract formation has been noted approximately $6\frac{1}{2}$ years following therapy. The second and third children presented with bilateral disease and were treated on 2 separate occasions with combinations of roentgen radiation and TEM. The disease recurred and despite enucleation, roentgen therapy, and systemic chemotherapy, the children died 2½ and 3 years after initial treatment. The fourth child presented with bilateral disease at 3 months of age. In August, 1960, one eye was removed and the other was treated with a good response. Four years later, a recurrent tumor was noted in a different area in the remaining eye. The patient has been retreated with radiation through a direct anterior port and with intra-arterial TEM. The tumor seems to be responding satisfactorily. The fifth retreated child presented with bilateral disease and an attempt was made to salvage both eyes. The tumor in the worse eye progressed and despite retreatment, enucleation had to be carried out. This patient was treated with TEM at the time of enucleation and, in retrospect, this was unwise as the child has had a persistent anemia, possibly due to excessive use of the drug.

RESULTS

Fourteen children have useful vision in I eye, I child has light perception only in the remaining eye and I child had the second eye removed for recurrent disease. Three have died of disease.

This series of 19 patients has been compared with a previous group of 19 patients treated at Charity Hospital from 1948 through June, 1958¹¹ (Table 1). In the earlier group, 17 had disease confined to 1 eye with 6 patients having extension into the nerve or orbit. Two had bilateral disease. Of this group treated by enucleation and/or irradiation, 7 are alive, 6 with useful vision, 12 having died of disease. Admittedly, further complications or deaths can be expected in the later group but thus far, the results are favorable.

COMPLICATIONS

The complications resulting from chemotherapy have been relatively minor. Nausea and vomiting have been of insignificant consequence. We have had 2 patients with serious problems with bone marrow depression. Both children had multiple courses of chemotherapy and irradiation. One had a leukopenia and anemia and has died of disease and I has a persistent anemia. Most of the children have had a drop in leukocyte count to a level between 2,500 and 4,000 white blood cells per cubic mm. when the drug was administered 7 to 10 times. These children

 $T_{\text{ABLE }} I \\$ Results of treatment of retinoblastoma

			Results				
		Unila	ıteral		Al	ive	
Period	Treatment	Intra- globular	Extra- globular	Bilateral	Useful Vision	No Vision	Dead
1948-58 1958-64	Excision and/or irradiation Excision and/or	11	6	2	6	I	12
	irradiation plus TEM	2	7	10	14	2	3

usually developed transient anemia as well.

The problem of cerebral damage from the drug must be considered; however, thus far, we have no definite evidence of damage. One child who subsequently died of brain involvement had clonic convulsions at home and later under observation, but we believe that this was due to cerebral involvement with tumor.

Complications arising from irradiation involving the eye or the surrounding orbital tissues have been noted. Of the 16 living patients, the first patient treated has early cataract formation. This child was treated on 2 separate occasions, once through an anterior port. Another child developed a vitreous hemorrhage in the remaining eye, possibly from irradiation, which resulted in loss of all vision except light perception.

Contracture of the orbit, fibrosis and pigmentation of the lid and overlying skin of the orbit have been a problem in some cases. The removal of an eye before the age of 6 will cause failure of growth of the orbit and technical difficulty in fitting a prosthesis. If the reaction from irradiation in the soft tissues makes the continuous wearing of a prosthesis difficult, the complications are compounded. Of the living children, 5 patients have problems of fibrosis of the lids and the skin about the orbit. These 5 patients were treated early in the series with higher doses of roentgen therapy and lower doses of chemotherapy.

DISCUSSION

The use of megavoltage irradiation as opposed to orthovoltage must be considered. There does not seem to be any disagreement that the preferable form of irradiation of retinoblastoma is with megavoltage. 12,17 This is particularly true for patients with the eye still present in whom a sharp beam with minimum skin reaction and limited scatter is desirable. However, when this study began, megavoltage radiation was not available; it was felt that, for the sake of comparable studies, the present program should be continued until

a group of patients could be accumulated for evaluation. We now plan to proceed to megavoltage therapy.

Consideration has been given to how the drug can be best administered. We have theorized that the administration of the drug immediately prior to or during irradiation might be of greater value than when the drug is given without relation to the irradiation. We are considering administering the TEM by a continuous intra-arterial infusion during the actual administration of the roentgen therapy. Experimental studies are planned to determine the value of this approach.

The use of increased tissue oxygen tension during the course of roentgen therapy has been shown to be of value.² With an

intra-arterial catheter present, it would be relatively simple to carry out a hydrogen peroxide infusion during the radiation therapy, thereby increasing the oxygen tissue tension. This will potentiate the action of the roentgen ray; however, the problem of associated complications must

no decision as to this approach.

CONCLUSIONS

be considered, and to date, we have made

Nineteen patients have been treated for retinoblastoma from July, 1958 through September, 1964, 10 with bilateral disease, 7 with unilateral disease involving the nerve or orbit, and 2 with unilateral disease confined to the globe. Sixteen patients are alive without evidence of recurrence, 14 with useful vision in one eye.

Irradiation with chemotherapy is recommended as primary treatment for retinoblastoma. Enucleation combined with TEM and irradiation should be reserved for patients in whom no useful vision can be salvaged or in whom the disease cannot be controlled by primary irradiation and chemotherapy.

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MODIFICATION OF RADIATION RESPONSE OF TUMORS BY ACTINOMYCIN D*

CLINICAL EVALUATION

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REATMENT of radioresistant tumors has been a major problem to the radiotherapist. Many chemical compounds have been investigated in the attempt to find substances which might preferentially increase the radiosensitivity of a tumor or decrease the radiosensitivity of the host. In 1959, D'Angio and co-workers reported a potentiation of the roentgen-ray effect by actinomycin D,3 and other authors subsequently confirmed this report.1,2,4,9,11 Initially, our patients were treated daily with the drug and with roentgen rays, and the times of these two therapies were not coordinated. When we were unable to observe the response reported by others, an animal tumor experiment was conceived. We investigated the effects of the combined treatment of actinomycin D* and radiation in a solid transplantable Walker tumor in rats.¹⁰ These experiments showed that the effect of the combined treatment depends on the time interval between drug administration and irradiation. Rapid tumor growth was noted when the tumor was irradiated 24 hours after the intraperitoneal administration of 150 µg./kg. actinomycin D, but marked regression of the tumor occurred if irradiation was performed 4 hours after actinomycin D injection.

The importance of this time interval was confirmed by studying a rapidly proliferating tissue—the hair follicle. The cellular damage to the anagen hair matrix of the mouse induced by combined actinomycin D

* Kindly supplied by Dr. Elmer Alpert of Merck, Sharp and Dohme Research Laboratories, West Point, Pennsylvania.

and radiation treatment was determined and related to the time of irradiation.6

Treatment of one patient with skin metastasis from a parotid epidermoid tumor suggested that the same time interval was also important in human tumors. Small portals were treated at different time intervals after administration of actinomycin D. A maximal response was noted 3 to 4 hours after injection of the

On the assumption that this time lapse of 3 to 4 hours might be effective in other tumors, we began to treat patients having. far advanced malignancies with the combination of actinomycin D and radiation. Adults were given intravenous injections of 500 μg. of actinomycin D followed after 3 to 4 hours by 5∞ rads to the tumor. This sequence was repeated twice weekly for 1 to 4 weeks until a total cumulative dose of 1,000 to 4,000 rads had been applied.

For comparative evaluations of the effects of drug and radiation alone, as well as the combined drug-radiation treatment, patients with well circumscribed metastases to both lungs were selected. In one group of these patients, treatments were given in the following sequence: (1) roentgen ray therapy to one lung, and (2) several weeks later, drug administration, followed by irradiation of the opposite lung. In the other group of patients, the sequence was reversed, being: (1) drug following irradiation to one lung, and (2) irradiation alone to opposite lung several weeks later. In

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Table I

ACTINOMYCIN D AND RADIATION THERAPY

	^	m . 1	
71	('nsec-	—Total	10000

- 10 cases excluded because
 - a. lost to follow-up
 - b. expired soon after treatment
 - c. recently treated

61 cases evaluated

- 16 cases no response to any treatment
- 14 cases response which could be due to irradiation alone or combined treatment
- 31 cases response due to combined treatment

addition, extrapulmonary metastatic lesions easily accessible to palpation or measurable by roentgenograms, as for instance bone lesions, were treated with a similar regimen.

Realizing the difficulties of evaluation of such clinical material, the following criteria were used:

- 1. All tumors were histologically proven before treatment was started.
- 2. Lesions treated with the differential regimen were compared grossly and histologically at autopsy, or
- 3. Objective measurements of the lesions were made on roentgenograms or by palpation 2 to 6 months after therapy.
- 4. When multiple lesions could not be compared, a total radiation dose known to be well below the tumoricidal range was used.
- 5. Subjective improvement was not considered.

We have treated 71 patients with this combined method. Tables 1 and 11 show the types of tumors treated and the results obtained with this treatment.

DISCUSSION

The mechanism of the potentiation of the radiation effect by actinomycin D and its time relationship may be based on the observation of Hackmann. Working with different tumors in mice, he found that a dose of 2 to 5 μ g. of actinomycin C produced an increase in the number of mitoses between 1 and 5 hours after administration of the

drug. During the subsequent 17 hours, the number of mitoses decreased, and had returned to normal by 22 hours after the time of injection. Tolmach and Terasima¹² have shown that mammalian cells vary in radiosensitivity during the cell cycle, the maximum sensitivity being reached during mitosis. It is, therefore, possible that the maximum effect of the drug and irradiation is

Table II
ACTINOMYCIN D AND RADIATION THERAPY

Histology	No. of Cases†
Neuroblastoma	-(2)
Osteosarcoma	-(3), **(2)
Liposarcoma	-(1)
Melanoma	-(2), **(1)
Myosarcoma	-(2), **(4)
Neurofibrosarcoma	-(I)
Leiomyosarcoma	-(1), *(1), **(1)
Wilms' tumor	-(2), *(2)
Teratocarcinoma of thymus	- (1)
Angiosarcoma	*(1)
Multiple myeloma	*(5), **(5)
Chondrosarcoma	*(1)
Adenocarcinoma of ovary	*(2), **(1)
Adenoacanthoma of ovary	*(1)
Adenocarcinoma of	• •
endometrium	**(1)
Synovial sarcoma	**(1)
Rhabdomyosarcoma	**(2)
Neurogenic sarcoma	**(1)
Hemangioendothelioma	**(ĭ)
Malignant meningioma	**(1)
Malignant mesothelioma	**(1)
Osteochondrosarcoma	**(1)
Undifferentiated sarcoma	、 ,
of orbit	**(I)
Mucoepidermoid carcinoma	` '
of parotid	**(I)
Squamous cell carcinoma	` '
of skin	**(1)
Squamous cell carcinoma	, ,
of lip	**(I)
Squamous cell carcinoma	• •
of mouth	— (1)
Squamous cell carcinoma	• •
of cervix	*(1)
Embryonal cell carcinoma	
of testis	**(2)
Carcinoma of rectum	**(1)
Teratocarcinoma of testis	**(1)

^{† (-)} no response to any treatment; (*) response which could be due to irradiation alone or combined treatment; (**) response due to combined treatment.

achieved when irradiation of the tumor coincides with a sensitive phase of the cell cycle.

According to Goldberg and co-workers,⁵ the actinomycin becomes attached to the guanine radical of the DNA. This inhibits a certain phase of the DNA dependent protein synthesis and may arrest cells in a certain stage of their growth cycle. The importance of the guanine radical was also pointed out by Kaplan and Zavarine⁸ who found that the sensitivity to irradiation of bacteria depends on the guanine content of their DNA.

Different human malignant tumors have variable growth rates. The time interval of 3 to 4 hours used in our studies for all tumors, therefore, may not be ideal for many of them. The sequence and timing of drug and irradiation is being studied in other cell populations in animals and in patients with advanced malignancies to clarify this question.

SUMMARY

Experiments on laboratory animals show that variation of the time interval between actinomycin D injection and administration of ionizing radiation modifies the radiation response of cells. Clinical studies suggest that certain radioresistant tumors, especially certain sarcomas, may exhibit enhanced radiosensitivity under similar conditions.

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PALLIATIVE TREATMENT OF METASTATIC TUMORS OF THE SOFT SOMATIC TISSUES WITH IRRADIATION AND CHEMOTHERAPY*

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THE palliative treatment of tumors of the soft somatic tissues presents a challenge to the physician who manages these patients in the final phase of their disease. Although of 418 patients with soft somatic tissue sarcoma, 39.2 per cent are living 5 years or more later, apparently cured,⁴ ultimately many patients require palliative therapy for these disease entities. Chemotherapy^{8,5,6,7} and irradiation² have been utilized for this purpose and have resulted in more effective control of the disease in these patients.

In this report the experience of the author in palliatively treating 23 patients with advanced metastatic tumors of the soft somatic tissues with irradiation and chemotherapy, in an effort to afford them greater comfort and longer survival, is described.

Most of the patients previously had adequate surgical treatment of their primary tumor and many had received irradiation following wound healing (Table 1). The patients ranged in age from 8 months to 66 years. There were 15 males and 8 females. There was 1 patient each with spindle cell sarcoma, synovial sarcoma, and fibroliposarcoma; 2 patients each with fibrosarcoma and myxoliposarcoma; 3 patients each with liposarcoma and neuroblastoma; and 5 patients each with rhabdomyosarcoma and leiomyosarcoma (Table 1).

TREATMENT AND DOSAGE

All of the patients presented with inoperable disease, and extensive further definitive surgery was deemed inadvisable (Fig. 1). Chemotherapy, in the form of actinomycin D intravenously, methotrexate orally, cyclophosphamide orally or intravenously, or chlorambucil orally, was

used in 21 patients; vincristine was used intravenously in 2 patients (Tables II and IV).

Actinomycin D was given intravenously either directly, avoiding tissue infiltration, or by injecting the drug into the rubber tubing of an intravenous infusion of 5 per cent dextrose in water running into a large arm vein. The dosage for adults was 0.5 mg. daily for 5 days. In the 8 month old child the dosage was 0.125 mg. daily for 5 days and in the 5 year old children it was 0.2 to 0.25 mg. daily for 5 days.

Methotrexate was given orally to adults in a dosage of 5.0 mg. daily for 5 days; 2.5 mg. was given daily for 5 days to the 8 month old and 5 year old children. Adults were given 200 mg. of cyclophosphamide orally daily for 5 days; the 8 month old baby was given 55 mg. orally daily for 5 days, and the 5 year old boys were given

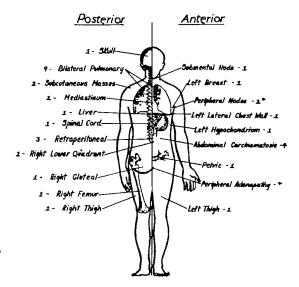


Fig. 1. The distribution and incidence of metastatic soft-tissue sarcomas in 23 patients.

^{*} Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8-10, 1965. From the Pack Medical Foundation, New York, New York.

 $Table\ I$ ${\tt PALLIATIVE\ TREATMENT\ OF\ 23\ PATIENTS\ WITH\ TUMORS\ OF\ THE\ SOFT\ SOMATIC\ TISSUES\ SEX,\ AGE,\ HISTOLOGIC\ DIAGNOSIS,\ AND\ PREVIOUS\ TREATMENT }$

Patient	Sex	Age (yr.)	Histologic Diagnosis and Location	Previous Treatment
1	M	31	Spindle-cell sarcoma of left thigh	Excision of tumor, April, 1962. Roentgen therapy, 2,900 r to thigh
2	M	52	Liposarcoma of left lower leg	Excision of tumor, radical groin dissection, April, 1956. Roentgen therapy 250 kv., 1,800 r to anterior port of left thigh, 1956. Thoracotomy metastasis in left lung, January, 1964
3	M	48	Fibrosarcoma of left upper arm	Left interscapulothoracic amputation, August, 1963. Roentgen therapy 250 kv., 3,600 r to left shoulder, lower neck
4	M	34	Liposarcoma of left lower leg	Cobalt 60 therapy, 5,000 r, April, 1962. Dissection of left calf, May, 1962. Cobalt 60 therapy to right lung, June, 1963
5	F	29	Fibrosarcoma of right hip	Excision, 1957. Roentgen therapy, 25c kv., 3,000 r to right hip. Re-dissection, 1959. Right sacroiliac hip disarticulation, right hemicolectomy, April, 1962
6	F	32	Synovial sarcoma of right thigh	Muscle group and right groin dissection, March, 1962. Roentgen therapy 250 kv., 2,100 r to right upper thigh
7	M	25	Rhabdomyosarcoma of right submandibular region	Local excision, December, 1961. Roentgen therapy, 250 kv., 3,000 r
8	M	58	Leiomyosarcoma, primary in duodenum, 1948	Excision, 1948
9	M	32	Rhabdomyosarcoma of right gluteal region	Local excision, 1960. Dissection of right gluteal, lumbar region, September 1962
10	M	8 mo.	Neuroblastoma of left suprarenal region	Excision of cervical lymph node, February, 1961
11	M	16	Embryonal rhabdomyosar- coma of right testis	Right orchiectomy, July, 1960. Roentgen therapy, 250 kv., central abdomen, 3,200 r anterior; 2,500 r posterior. Palliative removal of bulk disease
12	M	32	Liposarcoma of ileum	Wide excision of mass of right gluteal, November, 1957. Re-excision March, 1958. Roentgen therapy, 250 kv., 3,000 r anterior port of righ lower quadrant
13	F	21	Leiomyosarcoma of ileum	Excision of tumor of ileum, October, 1962. Re-exploration, June, 1964 inoperable
14	F	33	Leiomyosarcoma of stomach	Subtotal gastric resection, September, 1963
15	M	34	Fibroliposarcoma of left thigh	Hemipelvectomy, May, 1964
16	M	47	Myxoliposarcoma of left thigh	Excision of tumor, 1956
17	F	43	Myxoliposarcoma of left breast	Left radical mastectomy, September, 1961. Roentgen therapy, 120 kv 2,400 r to left anterior chest. Mitomycin C, 42 mg.
18	M	5	Neuroblastoma of left lung	Excision of right lung, July, 1960. Roentgen therapy, 250 kv., 2,500 r t right lung, dorsal spine
19	F	55	Leiomyosarcoma of uterus	Subtotal hysterectomy; colostomy, suprapubic cystostomy, March, 196
20	F	49	Leiomyosarcoma of uterus	Total hysterectomy, January, 1961. Cobalt 60 therapy, 2,400 rads to eac of 4 pelvic ports. Cyclophosphamide, unknown dose. Re-exploration January, 1964. Palliative removal of bulky lower abdominal mass
21	F	66	Rhabdomyosarcoma of left upper arm	Excision of left biceps tumor, November, 1959. Interscapulothoraci amputation, February, 1960
22	M	65	Rhabdomyosarcoma of left thigh	Massive soft-tissue dissection of left thigh in continuity with groin dis- section, December, 1962
23	M	5	Neuroblastoma of left pararenal region	Excision of right cervical lymph node, January, 1964. Roentgen therapy 250 kv., 2,500 r to left anterior abdomen; 2,500 r to para-aortic regio

50 to 95 mg. orally daily for 5 days. When chlorambucil was used in place of cyclophosphamide, 10 mg. orally was given daily for 5 days. Vincristine was given intravenously in a dosage of 0.05 mg./kg. at weekly intervals.

One to 7 courses of triple chemotherapy were given at intervals of 6 to 12 weeks, depending on the clinical status of the patient and the level of the hemogram.

Bone marrow aspiration or biospy was

performed in all patients prior to chemotherapy. Tumor cells were found in 2 patients: Patient 12, who had a liposarcoma, and Patient 14, who had a leiomyosarcoma.

A 250 kv. generator was employed for palliative roentgen therapy, generally giving 1,200 to 2,500 r in air by the fractionated technique to visible and palpable tumor. The daily dose per port ranged from 150 to 250 r in air. Each patient was carefully evaluated daily before therapy. If the

Table II

PALLIATIVE TREATMENT OF 23 PATIENTS WITH TUMORS OF THE SOFT SOMATIC TISSUES
EXTENT OF DISEASE AND TYPE OF TREATMENT

		At Beginning of Tr	eatment		Course
Patie	nt Date	Extent of Disease	Bone Marrow	Therapeutic Regimen	of Chemo- therapy
I	April, 1963	Bilateral pulmonary and liver metastases, recurrent tumor of thigh	Aspiration negative	Actinomycin D, 0.5 mg. intravenously daily×5. Methotrexate 5.0 mg. orally, daily×5. Cyclophosphamide 200 mg. orally, daily×5. Roentgen therapy, 250 kv. April, 1963: 2,000 r to right mandible, 2,000 r each to anterior and posterior left hip. December, 1964: 2,400 r to anterior and posterior right and left lungs	· •
2	January, 1964	Metastasis of left lung	Biopsy negative	Triple chemotherapy (as Patient I). Roentgen therapy, 250 kv. March, 1964: 2,400 r to lumbar spine, March, 1964: 2,500 r to posterior left chest. April, 1964: Sr [®] , 100 mc. June, 1964: Y ⁹⁰ microspheres, 15 mc	•
3	September, 1963	Metastases of left lateral chest wall	Aspiration negative	Triple chemotherapy (as Patient 1). Roentgen therapy, 250 kv. October, 1963: 3,000 r to left lateral chest. January, 1964: 30 mc Y ¹⁰ microspheres to left thorax. June, 1964: 200 mc Y ¹⁰ microspheres to left thorax	
4	January, 1964	Metastases of left and right lungs	Aspiration negative	December, 1964: 25 mc Y ¹⁰ microspheres. January, 1965: triple chemotherapy (as Patient 1). Cobalt 60 teletherapy left lung; 2 mc P ²⁸	
5	May, 1963	Recurrence in right lower quadrant	Aspiration negative	Triple chemotherapy (as Patient 1). Roentgen therapy, 250 kv., 3,000 r to anterior and posterior right lower quadrant. October, 1963, November, 1963: 75 mc Y microspheres	
6	January, 1963	Bilateral pulmonary metastases; recurrence in right thigh	Aspiration negative	Triple chemotherapy (as Patient 1). January, 1963, September, 1963: 20 mc Y ⁵⁰ microspheres. December, 1963: Roent-gen therapy, 250 kv., 2,800 r to right thigh, 2,400 r each to anterior and posterior right and left lungs	-
7	April, 1962	Bilateral pulmonary metastases	Aspiration negative	Actinomycin D, 0.5 mg., intravenously, daily×5. Methotrexate 5.0 mg. orally, daily×5. Chlorambucil 10 mg. orally, daily×5. Roentgen therapy, 250 kv. June, 1962: 1,800 r posterior lungs. September, 1962: 1,200 r to posterior left lung. July, 1963: 1,800 r to anterior and posterior mediastinum. December, 1963: 1,800 r to anterior right and left lungs. February, 1964: 20 mc Y ¹⁰ microspheres	•
8	February, 1964	Bilateral pulmonary metastases; metastasis of right femur	Aspiration negative	February, 1964: Vincristine 0.05 mg./kg., intravenously. Vincristine 0.075 mg./kg. intravenously. April, 1964: triple chemotherapy (as Patient 1). Roentgen therapy, 250 kv., 3,000 r to anterior and posterior right lung	;
9	October, 1964	Axillary, inguinal lymphadenopathy; retroperitoneal disease	Aspiration negative	Triple chemotherapy (as Patient 1). Roentgen therapy, 250 kv., 1,800 r to posterior lumbar region	r
10	February, 1961	Mass of left hypochon- drium; hydrocephalus; subcutaneous sub- mental node	Aspiration negative	Actinomycin D, 0.125 mg., intravenously, daily×5. Methotrexate 2.5 mg. orally, daily×5. Cyclophosphamide 50 mg. orally, daily×5. Roentgen therapy, 250 kv., 2,500 r to left hypochondrium, 600 r each to right and left lateral skull, 1,200 r to right groin, 1,200 r each to right and left axillae, 1,200 r to left thigh	: :
11	June, 1962	Huge retroperitoneal mass	Aspiration negative	Triple chemotherapy (as Patient 1). Roentgen therapy, 250 kv., 1,800 r to anterior and posterior right and left pelvic ports	
12	April, 1963	Multiple subcutaneous nodules; recurrent mass in right gluteal region	Aspiration positive	Triple chemotherapy (as Patient 1). Roentgen therapy, 250 kv., 2,100 r to anterior and posterior right lower quadrant; cone therapy—1,200 r to larger nodules	

Table II (continued)

			At Beginning of Tre	atment		Courses
Patier	ıt	Date	Extent of Disease	Bone Marrow	Therapeutic Regimen	of Chemo- therapy
13	June,	1964	Abdominal carcino- matosis	Aspiration negative	Actinomycin D, 0.5 mg., intravenously, daily×5. Methotrexate 5.0 mg. orally, daily×5. Chlorambucil 10 mg. orally, daily×5. Roentgen therapy, 250 kv., 2,100 r to right and left anterior pelvis; 2,100 r to sacral region	
14	June,	1964	Abdominal carcinomatosis	Aspiration positive	Triple chemotherapy (as Patient 13). Roentgen therapy, 250 kv., $2,400$ r each to 4 abdominal ports	1
15	June,	1964	Retroperitoneal disease	Aspiration negative	Triple chemotherapy (as Patient 13). Vinblastine 0.01 mg./kg., intravenously. Roentgen therapy, 250 kv., 2,400 r to anterior and posterior para-aortic region, 1,800 r to left temporal region. November, 1964: 15 mc Y ⁹⁰ microspheres to brain and lung metastases. December, 1964: Roentgen therapy, 250 kv., 1,200 r to cervical spine	
16	April,	1962	Disease of left breast, mediastinum and pelvis	Aspiration negative	Triple chemotherapy (as Patient 1). Roentgen therapy, 250 kv., 1,800 r to posterior mediastinum, 1,600 r to left breast, 2,000 r each to 4 anterior abdominal quadrants, 1,600 r to lumbar spine	,
17	June,	1962	Mass in left lung	Aspiration negative	Triple chemotherapy (as Patient 13). Cobalt 60 teletherapy, 2,400 rads to left lung	. 2
18	Septe	mber, 1960	Bilateral pulmonary metastases; spinal cord compression (para- plegia). Skull metas- tases, June, 1961	Aspiration negative	Actinomycin D, 0.25 mg., intravenously, daily×5. Methotrexate 2.5 mg. orally, daily×5. Cyclophosphamide 95 mg. intravenously, daily×5. 1961: Roentgen therapy, 250 kv., 2,500 r to posterior left lung, 1,800 r to dorsal spine, 1,500 r to vertebrae and skull	i
19	Marc	h, 1964	Abdominal carcinomatosis	Aspiration negative	Vincristine 0.05 mg./kg. intravenously, weekly×3	1
20	Febru	ary, 1964	Abdominal carcino- matosis	Aspiration negative	Vincristine 0.05 mg./kg. intravenously, weekly×3. Cobalt 60 teletherapy, 4,072 rads tumor dose to anterior port of lower abdomen and pelvic port	
21	June,	1961	Bilateral pulmonary metastases	Aspiration negative	Triple chemotherapy (as Patient 1). Roentgen therapy, 250 kv., $1,800$ r to posterior right and left lungs	I
22	Marci	h, 1963	Multiple subcutaneous and bilateral pulmo- nary metastases	Aspiration negative	Triple chemotherapy (as Patient 1). Roentgen therapy, 250 kv., 2,400 r to posterior right and left lungs	2
23	Febru	ary, 1964	Mediastinal metas- tases; peripheral lymphadenopathy	Aspiration negative	Actinomycin D, 0.2 mg., intravenously, daily×5. Methotrexate 2.5 mg. orally, daily×5. Cyclophosphamide 50 mg. orally, daily×5. Roentgen therapy, 250 kv., 2,000 r each to anterior and posterior mediastimum, 1,500 r each to right and left supraclavicular regions, 2,000 r each to right and left groins	

white blood cell count was less than 2,500 cells or the platelet count below 75,000 cells/cu. mm. of blood, therapy was temporarily withheld until these levels were attained. Three patients received cobalt 60 teletherapy.

Irradiation was given to relieve pain, reduce bulky disease, and, over ulcerated regions of disease, to promote healing. Chemotherapy was used in 9 patients prior

to radiation treatment. Palliative irradiation was initially given to 10 patients after the first course of chemotherapy; in 4 patients radiation was given simultaneously with chemotherapy. The clinical status of the patient, including the hemogram, was the determining factor in the sequence of treatment.

Seven patients were also given radioactive isotopes in the form of yttrium 90

 $\begin{tabular}{ll} Table \ III \\ PALLIATIVE TREATMENT OF 23 PATIENTS WITH TUMORS OF THE SOFT SOMATIC TISSUES \\ RESULTS OF TREATMENT \end{tabular}$

Pa- tient	Resnonce	Duration of Control (mo.)	1 Toxicity	Remarks
1	Healing of ulcerated hip; control of	10	Alopecia; leukopenia;	Comfortable until sudden death at home, February,
2	lung disease until December, 1963 Control of disease of left breast; free of pain in lumbar spine	8	bronchopneumonia Alopecia; leukopenia	Homologous serum hepatitis, July, 1964; probable liver metastasis. Died September, 1964
3	Control of disease; free of pain until April, 1964	7	Alopecia; leukopenia	Respiratory death, May, 1964. Necropsy: lung, liver metastases
4	Good response until December, 1964	11	None	Comfortable until December, 1964. Died February, 1965
5	Good control until December, 1964	7	Alopecia; leukopenia	Free of pain, comfortable until December, 1963. Died January 2, 1964
6	Good control until December, 1964	11	Leukopenia; broncho- pneumonia	Respiratory decompensation, January, 1964. Died February, 1964
7	Excellent response until November, 1963	21	Leukopenia, alopecia, oral toxicity	Progressive pulmonary insufficiency, November, 1963. Probable pulmonary embolus; sudden death, March 9, 1964
8	Control of hemoptysis and pain	4	Leukopenia	Died at home, June, 1964
9	Good control of pain and disease	3	None	Necropsy January, 1963: rhabdomyosarcoma of heart, lungs, pancreas, lymph nodes, retroperitoneum, left adrenal, thyroid, skull, inferior vena cava
10	Good regression until August, 1963	35	Leukopenia; alopecia	Died January, 1964. Widespread disease of lungs, brain, liver and skeleton
11	Regression of disease	8	Leukopenia; alopecia	Necropsy: metastases to liver, lungs, spleen and retro- peritoneum. Amyloidosis of kidney
12	Regression of bulky disease	6	Leukopenia; alopecia	Died at home
13	Excellent control of disease	9+	Oral toxicity; leukopenia	Partial intestinal obstruction, January, 1965. Living and well
14	No clinical response	none	Leukopenia	Intestinal obstruction, paraplegia, and spinal metastasis. Died
15	Regression of disease	7	Leukopenia	Died December, 1964. Brain, lung and retroperitoneal metastases
16	Regression of disease	24	Leukopenia	Diabetes mellitus beginning April, 1963. Died April, 1964
17	Control of lesion of left lung	33+	Leukopenia	Still well; free of active disease
18	Control of pulmonary lesion; improved leg motion; partial return of rectal sphincter control	11	Leukopenia	Free of pain; increased strength; improvement in paraplegia. Died October, 1961
19	None	none	Leukopenia	Died suddenly 1 wk, after last treatment. Necropsy: bronchopneumonia, peritonitis and tumor invading ileum
20	Control of metastatic disease	13+	Leukopenia; neuro- pathy	Living; free of active disease
21	Relief of pain; improved breathing	3	Leukopenia	Died at home September, 1961
22	Minimal regression	3	Leukopenia	Died June, 1963. Widespread metastases
23	Progressive after September, 1964	7	Leukopenia; alopecia	Died December, 1964. Widespread metastases

microspheres. These were administered for pulmonary metastases (5 patients) or by intracavitary instillation (1 patient) or interstitially (1 patient) by Dr. Irving M. Ariel as supplemental therapy to control the disease. One patient (Patient 2), with painful skeletal metastases, was given 100 mc of strontium 85, with relief of bone pain. These materials were used when conventional radiation therapy did not control the disease; when bulky tumor masses previously irradiated did not respond to mea-

sures to control pain, or when further systemic therapy could not be given owing to leukopenia and/or thrombocytopenia (Ta ble 11).

RESPONSE

Of the 23 patients, 21 derived a beneficial clinical response from the palliative therapy (Table III). In 2 (Patients 14 and 19) there was no significant clinical response. The duration of clinical control varied from 3 to 35 months. Three pa-

tients were relieved for 3 months; I each for 4 and 6 months; 4 for 7 months; 2 for 8 months; I for 10 months; 3 for 11 months, and I each for 21, 24, and 35 months. Patients 13, 20, and 17 are alive and free of active disease at 9, 13, and 33 months, respectively.

Figure 2 shows the healed ulcerated hip region of Patient I after treatment; Figure 3, A and B shows control of the metastatic fibrosarcoma of the lateral chest wall of Patient 3; and Figure 4, A and B shows the resolution of the bilateral pulmonary metastases that was obtained in Patient 7 with irradiation and chemotherapy.

TOXICITY

Alopecia occurred in 9 patients; leukopenia in 21 patients, and bronchopneumonia in 2 patients. Peritonitis was found



Fig. 2. Patient 1. Healed hip region, previously deeply ulcerated, following irradiation with 2,000 r (in air) each to an anterior and a posterior port. Triple chemotherapy was given concomitantly.

TABLE IV

COMBINED PALLIATIVE TREATMENT OF 23 PATIENTS WITH TUMORS OF THE SOFT SOMATIC TISSUES

Treatment	No. of Patients
Chemotherapy	
1. Actinomycin D 0.125-0.5 mg.	
intravenously, daily \times_5	
Methotrexate 2.5–5.0 mg.	
orally, daily \times 5	
Cyclophosphamide 50-200 mg.	
orally, daily	16
or	
Actinomycin D Methotrexate as above	
Chlorambucil 10 mg. orally, daily	5
2. Vincristine 0.05 mg./kg.	,
intravenously	2
[rradiation	
1. Orthovoltage roentgen therapy,	
250 kv., 1,300–3,000 r	19
2. Cobalt 60 teletherapy	3
3. Y ⁹⁰ microspheres	3
5. I microspheres	/

at necropsy in I patient in whom the tumor had invaded the ileum. A temporary peripheral neuropathy, with paresthesias of the arms and hands, occurred in I patient receiving vincristine.

SUMMARY

Twenty-three patients with advanced metastatic soft-tissue sarcomas were palliatively treated with chemotherapy and irradiation with beneficial response in 21, the duration of the clinical control varying from 3 to 35 months.

Chemotherapy and irradiation appear to be useful modalities in the palliative control of metastatic sarcomas of the soft somatic tissues.

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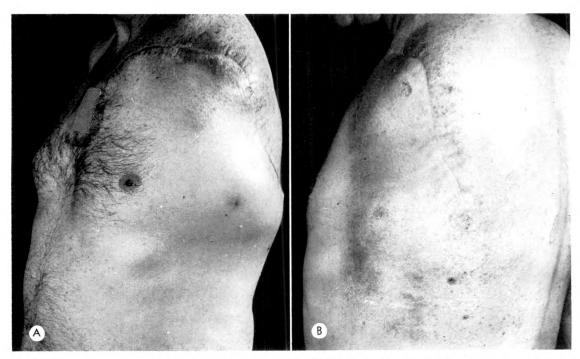


Fig. 3. Patient 3. Metastatic fibrosarcoma of the chest wall. (A) Before treatment with triple chemotherapy and irradiation. (B) After treatment.

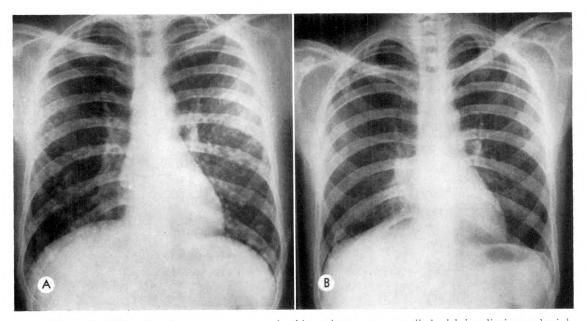


Fig. 4. Patient 7. Bilateral pulmonary metastases in this patient were controlled with irradiation and triple chemotherapy from (A) June, 1962 until (B) November, 1963.

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THE VALUE OF CHEMOTHERAPY IN THE IRRADIATION OF OVARIAN CARCINOMA*

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THE results of radiotherapy in ovarian carcinoma have not been greatly enhanced by the introduction of newer radiation techniques and modalities. This is particularly true in the case of the more advanced stages of the disease where it has spread beyond the pelvis. Since the amount of radiation that can be safely administered to the abdomen is limited, the authors have sought a means to supplement the tumoricidal effect of radiation upon such lesions.

Various chemotherapeutic agents have been tried in the past, among which triethylene thiophosphoramide (Thio-TEPA), a polyfunctioning alkylating agent, appears to be one of the most effective. The fact that Thio-TEPA is known to have no unfavorable effect upon the kidney contributed to its selection as the agent of choice in this study. However, since Thio-TEPA does impair hematopoiesis, in order to minimize treatment interruptions, it was decided to withhold its administration, if possible, until the start of the course of radiation therapy.

Fifty-eight patients have received chemotherapy concomitantly with roentgen radiation for ovarian carcinoma at the Albert Einstein Medical Center since this program was first instituted in December, 1958, through April, 1964. Forty-six patients received cobalt 60 teletherapy at the Northern Division of the institution; the remainder were treated at the Southern Division where only orthovoltage facilities were available. The series at the Northern Division was made up of consecutive cases until June, 1961, after which date some

cases received chlorambucil instead of, or in addition to, Thio-TEPA, while several were treated only by radiation. Although all of the cases referred during the above dates, aside from the latter, were treated by the combined approach, a review of admission records indicates that only about half of the patients in whom the diagnosis of ovarian carcinoma was made in this institution were referred for radiotherapy. In light of the predominance of advanced states in the present series, it is likely that most of the cases treated by surgery alone had less extensive disease. Surgical procedures on the cases in this series have varied from a limited biopsy to panhysterectomy, omentectomy, and local bowel resection.

TREATMENT PROGRAM

Patient treatment was guided by the following protocol:

(A) RADIATION THERAPY

All cases receive a *full* course of irradiation to the pelvis or abdomen, or both, as required by the gross extent of disease. The tumor dose varies with the quality of radiation used. Cases treated with cobalt 60 receive 5,000 r in 5 elapsed weeks throughout the pelvis if the tumor appears confined to this region. Cases with abdominal dissemination are given 3,000 r to both the pelvis and the entire abdomen concurrently during a 6 to 7 week period. Special care is taken to treat the entire abdomen up to the diaphragms, including the liver and both kidneys. Two anterior and two posterior opposing portals, averaging 20 by 17 or 18 cm., are usually treated either anteriorly or

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Histopathology	Clinical Stage						
	I	IIa	IIb	III	IV	V	Total
Adenocarcinoma							
Serous		3	I	2	16	4	26
Mucinous		•			I		I
Mixed*		2			6	I	9
Undifferentiated			I		4		5
Other†			3		3		6
Not Classified		1	_	I	3	2	7
Total		6	5	3	33	7	54

TABLE I
CLASSIFICATION OF ALL CASES TREATED

posteriorly on the same day. When treatments are administered with orthovoltage roentgen rays,* 4,000 to 4,500 r in 4 or 5 weeks' time are given to the pelvis through four converging fields. When required, the pelvis and lower abdomen receive approximately 3,000 r (midplane dose) in 4 weeks' time, followed by 2,300 r to the entire upper abdomen during the ensuing 4 to 5 weeks.

(B) CHEMOTHERAPY

- r. Thio-TEPA. A total dose of 0.8 mg./kg., intravenously, is given in 5 mg. daily doses starting the first day of irradiation. In the presence of ascites, diffuse peritoneal seeding or spillage of cystic contents, 0.5 mg./kg. is instilled intraperitoneally at the time of surgery or as soon as possible thereafter through in-dwelling polyethylene tubes. An additional 0.5 mg./kg. is then given, intravenously, in 5 mg. daily doses as described above.
- 2. Chlorambucil (Leukeran) is given orally in 0.2 mg./kg. divided daily doses and continued as long as the blood picture permits. This course is usually repeated intermittently.
- 3. 5-Fluorouracil (5-FU) was given in only several cases after recurrence in doses

of 15 mg./kg./day, intravenously, for 3 days followed by 7.5 mg./kg./day until toxicity appeared. This may be repeated at 4 to 6 week intervals if initially successful.

RESULTS

As stated, most of the patients in this series already had widespread disease when referred for treatment. Cases completing the prescribed course of combined therapy are classified in Table I according to their histopathology and clinical staging (Table II) when first seen. All di-

Table II
CLINICAL STAGING OF OVARIAN CARCINOMA*

Stage	I Tumor confined to one ovary and believed
	to have been completely removed sur-

Stage II No clinical evidence of residual disease following surgery, but—

- a) Tumor extends to surrounding pelvic structures and may or may not have been totally excised
- b) Spillage with contamination occurred during removal of cystic tumor
- Stage III Clinical evidence of residual pelvic disease after surgery
- Stage IV Extrapelvic extension (including ascites)
 Stage V Recurrence of disease present at the time
 patient is first seen (at least 1 year after
 original treatment)

^{*} Includes partly solid, and mixed serous and mucinous tumors.

[†] Includes mesonephric, granulosa cell, and endometrial cell tumors.

^{*} All patients at the Southern Division, AEMC, were treated with 250 kvp., Thoraeus 3 filtration, 30 ma., 50 cm. target skin distance, 3.0 mm. Cu half value layer.

^{*} Modified from Murphy.17

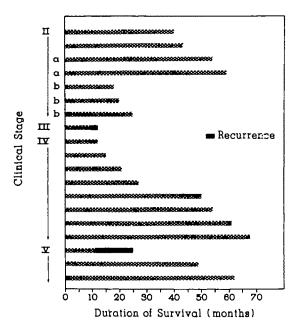


Fig. 1. Surviving patients treated with Thio-TEPA and irradiation.

agnoses were confirmed histologically. Four individuals originally starting treatment were unable to complete the planned treatment course due to their rapidly deteriorating condition and have been excluded from this evaluation. Two others are included although they barely survived the course of combined therapy. None has been lost to follow-up.

The initial response to treatment in this series was almost invariably favorable. All but 2 of the 21 cases with clinically detectable tumor after surgery demonstrated objective evidence of tumor regression at the conclusion of radiation therapy. This is a significantly greater proportion than has been reported following the administration of Thio-TEPA alone.

SURVIVAL

Nineteen of 44 patients* treated with Thio-TEPA and radiation are still living, and with 2 exceptions remain clinically free of disease (Fig. 1). Survival times in this group at present range from 12 to 63 months following the start of treatment.

Only 6 of these patients have been followed less than 2 years.

On examining the survival of patients who have already succumbed to their disease (Fig. 2), it is apparent that all recurrences took place within 2 years. This observation does not alter the fact that ovarian carcinoma may occasionally recur considerably later, but it does suggest that some impression of the value of combined therapy may be gained from the above group. All deaths are assumed to be due to neoplasm, although in at least 2 instances there was no clinical evidence of recurrent disease immediately prior to death. One patient died in congestive failure, 49 months after treatment.

The mean survival of those now dead was 15.6 months. It is noteworthy that this interval was, on the average, 6.1 months after tumor was first discovered to have recurred (Fig. 2). This further prolongation of survival can be ascribed, at least in part, to responses to subsequent courses of chemotherapy. Seven of 10 patients receiving a second course of Thio-TEPA intravenously again had objective evidence of benefit which then persisted from 2 to 13 months.

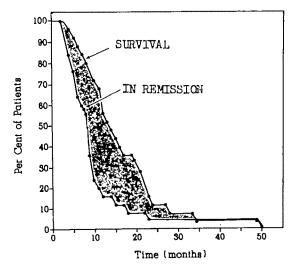


Fig. 2. Duration of original remission and survival time in 25 patients after Thio-TEPA and irradiation. The patient who survived 49 months after treatment died in congestive failure.

^{*} The first 42 of these were patients referred consecutively.

5-Fluorouracil (5-FU) was used sucessfully in 5 of 8 cases with recurrent neoplasm. Although responses to this antimetabolite were generally more short-lived, the fact that they occurred at all is significant, inasmuch as these patients had already demonstrated refractoriness to repeated courses of Thio-TEPA.

Ten patients were given chlorambucil orally as the primary form of drug therapy (Table III). In most instances this followed the intraperitoneal instillation of Thio-TEPA. Only a single patient treated in this manner is still living without disease. A second survivor was found to have recurrence II months after her original treatment, and the remaining 8 patients are now dead, the longest survival among them being 27 months. Chlorambucil was also tried in several patients who did not originally respond to intravenous Thio-TEPA but in these instances it, too, was ineffectual. No fair comparison can be made with the previously described cases because of different clinical stages constituting the 2 groups, and the relatively small number so treated.

MORBIDITY

The most frequent early manifestation of Thio-TEPA toxicity was hematopoietic in character. A depression of the peripheral white blood cell count and hemoglobin typically appeared I to 2 weeks following completion of the course of parenteral therapy. Thrombocytopenia was often observed shortly thereafter, but was rarely of equal degree.

In anticipation of such changes, complete blood cell counts were done weekly on all patients, and more frequently as warranted by findings. Treatments had to be temporarily withheld because of leukopenia (less than 2,000 per cu. mm.) in 8 patients, 5 of whom had received Thio-TEPA both intraperitoneally and intravenously. Although all but one of this group were irradiated over their entire abdomen as well as pelvis, the timing of leukopenia appeared to correlate more closely with chemotherapy than with irradiation.

Table III
RESULTS IN PATIENTS RECEIVING CHLORAMBUCIL
WITH RADIOTHERAPY

Patient	Clinical Stage	Duration of Remission (mo.)	Total Survival (mo.)
E.B. B.S.	V IV	13	17 15*
M.F.	IIa	3	17
F.H.	IV	14	15
A.A.	IV	I	I
F.E.	IV	20	27
C.A.	IV	10	11
B.M.	IV	3	3
M.M.	V	11	13†
S.S.	IV	4	4

^{*} Alive and clinically free of disease.

Treatment interruptions never exceeded I to 2 weeks with the exception of I patient who inadvertently received considerably more than the prescribed amount of Thio-TEPA. No delayed or persistent hematopoietic damage has been observed. It is noteworthy in this connection that 2 years later the overtreated patient described is clinically free of disease and has a normal blood picture.

One case with recurrent advanced neoplasm died in marrow failure secondary to 5-FU, and another following chlorambucil. However, no toxic deaths have been either directly or indirectly attributed to Thio-TEPA.

Several patients developed diarrhea during the course of combined therapy, but in only 2 instances did the severity of this symptom require interruption of treatment. Tolerance of the gastrointestinal tract was generally equal to that which could be anticipated in individuals receiving similar radiation treatment alone. A rectovaginal fistula developed in 1 case 2 months following pelvic irradiation. This patient had been given 6,000 r during 45 elapsed days because of recurrence at the vaginal vault I year after panhysterectomy for ovarian carcinoma. The fistulous tract when excised was found to contain residual invasive tumor.

[†] Alive with recurrent disease.

Table IV

FREQUENCY OF OBJECTIVE RESPONSE
TO THIO-TEPA ALONE

Author	No. Treated	No. Respond- ing	Proportion Responding
Shay and Sun ²⁵ Munnell et al. ¹⁶ Ultmann et al. ²⁷ Bateman ² Hreshchyshyn ⁶ Samuels et al. ²²	3 17 27 96 21 37	2 14 13 44 6 25	66.6% 82.3% 48.2% 45.8% 28.6% 67.6%
Total	201	104	51.2%

No clinical evidence of radiation nephritis in the form of hypertension or abnormal urinary findings has thus far been encountered in the 23 patients who received total abdominal as well as pelvic irradiation. Also, there has been no increase of wound infections, dehiscences, or other surgical complications as a result of these treatments.

DISCUSSION

Although radiotherapy is generally regarded as a useful adjunct to surgery in the treatment of ovarian malignancy, 4.6,10,11,21 some evidence exists to the contrary. 3,19 Chemotherapeutic trials have been motivated by the poor results often achieved with either surgery and irradiation, or both.

A number of different alkylating agents have been reported to produce remissions in ovarian carcinoma, including triethylene melamine (TEM),^{4,9,26} nitrogen mustard,^{9,22} cyclophosphamide,^{9,22} and hemisulfur mustard.⁷ Samuels and co-workers²² found l-sarcolysin and Thio-TEPA more effective than cytoxan and nitrogen mustard.

Shay et al.²⁴ first described the efficacy of Thio-TEPA in the treatment of leukemia. Reports of the value of this agent in ovarian carcinoma followed soon thereafter,^{1,25} and there have been many confirmatory reports since. Objective responses

occurred in somewhat over half of the cases in these studies (Table IV), and usually persisted less than a year.

It is reasonable to expect 2 forms of treatment, possibly differing in their modes of action but each capable of producing benefit alone, to produce greater benefit together, provided their combined toxicity is not prohibitive. Indeed, it has been found that chemotherapy combined with irradiation may improve results obtained in squamous cell carcinomas of the head and neck^{5,13} and, possibly, in lung cancer.²⁸

The ideal chemotherapeutic agent for any such combined approach is one which does not compromise the amount of radiation which can be safely administered. Thio-TEPA meets this requirement. It has been found to have no unfavorable effect on the kidneys,25 the organ whose radiosensitivity is the major limiting factor in abdominal irradiation. This impression has been corroborated in the present study. Another advantage of Thio-TEPA is that it is not particularly irritating to normal tissues at the site administered, and accordingly, unlike nitrogen mustard, it does not interfere with wound healing. Also, in contrast to cytoxan, it rarely causes alopecia.

Both Kottmeier¹² and the authors²³ have previously described encouraging preliminary results with Thio-TEPA and irradiation combined in ovarian carcinoma. Chlorambucil has been similarly used by Miller and Brenner¹⁵ to produce remissions in 16 of 19 patients which had persisted 3 to 23 months at the time reported. These workers noted that lengths of survival in these patients were longer than that achieved with either modality alone. Others¹⁸ have also observed that remissions are more likely with this approach.

It is pointless to make comparisons with results reported using other approaches because of the large element of case selection and the relatively short follow-up periods in the present series. However, the high proportion of initial responses and the fact that 8 of 26 Stage IV cases receiving Thio-

TEPA plus radiation still survive (Fig. 1)* contrast favorably with the results obtained here without the benefit of chemotherapy in previous years (Table v). Only 5 of 17 Stage III and IV cases irradiated at the Southern Division of this institution without chemotherapy from 1951 through

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1960 survived longer than I year, the longest survival among these being 20 months (Table v). Southern Division patients irradiated with orthovoltage roentgen rays and receiving chemotherapy have tolerated their treatment as well, and have continued to do at least as well as those receiving cobalt 60 radiation. It is also noteworthy that 3 of 5 patients initially treated for recurrence (Stage v) are living

The administration of 3,000 r to the abdomen was undertaken only after considerable deliberation and with much concern over the possibility of late effects upon the kidneys. It was concluded that the risk was warranted. Most of the radiologists polled by Rubin et al.²¹ subscribe to a similar point of view.

25 to 62 months after combined therapy.

Kottmeier¹² takes issue with the oftquoted dictum that as much tumor as possible should be excised, on the grounds that the uterus provides a convenient receptacle for radium sources, thereby facilitating pelvic irradiation. Unfortunately, such an approach cannot be expected to benefit abdominal carcinomatosis. Meigs¹⁴ advocates that at least complete hysterectomy, bilateral salpingo-oophorectomy and total omentectomy be carried out when possible, and Kent and McKay¹⁰ report that their best results over the years have been gained where the uterus, ovaries, and as much gross tumor as possible were excised and roentgen radiation then administered. Since the extent of disease and technical resectability were frequently deciding factors in determining the extent of surgery in the present series, it may or may not be significant that no patient in

Table V

Advanced cases treated at southern division without chemotherapy (1951–1960)

Patient	Clinical Stage	Duration of Remission (mo.)	Total Survival (mo.)
A.L.	Ш	6	6
M.C.	\mathbf{III}	4	9
N.D.	IV	12	12
M.C.	IV	9	9
E.B.	IV	6	13
P.C.	IV	7	14
F.K.	IV	7	7
K.Z.	IV	3	4
L.W.	IV	I	ĭ
S.W.	IV	6	9
L.R.	IV	13	13
S.E.	IV	6	6
F.R.	IV	8	8
F.S.	IV	20	20
I.R.	IV	3	4
R.R.	IV	15	15
A.G.	IV	3	3

whom the procedure was limited to biopsy is still living.

INFLUENCE OF HISTOLOGY AND CLINICAL STAGE

Rubin²⁰ has called attention to the correlation between microscopic appearance and clinical staging and the eventual outcome in ovarian cancer. The consensus is that radiosensitivity cannot be predicted on the basis of histopathology alone.4,8,12,21 In this series 4 of the 5 cases of undifferentiated carcinomas were clinically staged as IV and all died within II months. On the other hand, 2 of 3 cases which were only partially undifferentiated, I a Stage v and the other a Stage IV, remain clinically free of disease, 4½ anc more than 5 years after treatment, respectively. Two mesonephric tumors and one mucinous carcinoma case have also done exceedingly well in contrast to the poor results obtained by Samuels et al.,22 using alkylating agents alone. The presence of liver involvement and large, matted abdominal tumor augured poorly in the present series, all 8 such cases developing recurrences within a year. How-

^{*} All but 3 have survived more than 2 years following treatments.

ever, 3 such patients were carried 22, 22, and 33 months respectively with repeated courses of chemotherapy, and a fourth is still alive at 15 months.

ROUTE OF ADMINISTRATION

Inasmuch as Thio-TEPA is effective systemically, there is some question regarding the value of intracavitary administration. Bateman² has found direct injections into tumor masses very effective. Twentythree patients in the present series had intraperitoneal instillations, mostly because of ascites and in a few instances following the inadvertent spillage of cystic contents. The reappearance of fluid was prevented in most of these cases, but since they also received total abdominal irradiation and Thio-TEPA intravenously, it cannot be assumed that the benefit was due exclusively to *intraperitoneal* administration. Two patients who received this compound intrapleurally as well as intravenously have now survived 25 and 61 months. The authors are continuing to use the intraperitoneal route in all cases of ascites except in the presence of large abdominal tumor masses which subdivide the peritoneal cavity into compartments.

CONCLUSIONS

The results thus far achieved in treating ovarian carcinoma by a combined chemotherapeutic-radiation approach in addition to surgery, appear better than those obtainable in the past. The toxicity due to this vigorous approach has, generally, been well tolerated. A major advantage of using Thio-TEPA in addition to radiation has been the increased incidence and prolongation of remissions. Such initial use of chemotherapy has not prejudiced its efficacy in the event of subsequent recurrence. The fact that patients who received chlorambucil have not fared as well as those receiving Thio-TEPA may be related to the higher proportion of advanced stages in this group.

Further studies utilizing large random-

ized series are required to substantiate the above impressions.

SUMMARY

- 1. Combined chemotherapy and irradiation has been administered to 58 ovarian carcinoma patients, most of them advanced cases, from 1958 through 1964.
- 2. Nineteen of 44 patients who received Thio-TEPA plus irradiation still survive as long as 12 to 68 months after the start of treatment.
- 3. Patients who subsequently developed recurrences usually responded to a second course of chemotherapy.
- 4. These results, as well as the duration of the original period of remission, are an improvement over those previously obtained without the benefit of chemotherapy at this institution.
- 5. The additional morbidity associated with this approach is deemed acceptable.

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COMBINED THERAPY IN MALIGNANT LYMPHOMA*

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*HE availability of newer chemotherapeutic agents and increasing experience in their use in combination with radiation therapy for the treatment of lymphoma warrant a brief review at this time. In this presentation, certain aspects in the treatment of Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma are discussed. Drugs which are considered include alkylating agents, the periwinkle alkaloids (vinblastine and vincristine) and methylhydrazine. Although the generally accepted methods of treating lymphoma have not changed significantly since Karnofsky et al.10 reviewed the subject before the American Radium Society several years ago, certain developments are worthy of mention. The problem of hyperuricemia associated with rapid lysis of tumor has been greatly reduced with the use of xanthine oxidase inhibitor (Allopurinol) as shown by Krakoff and Meyer. In Although careful observation of blood for development of leukopenia or thrombocytopenia is mandatory in treatment of these diseases, the marrow depressing effect of vinblastine (Velban) in therapeutic dosage does not appear to be as great as that observed when aklylating agents are employed. It must be emphasized that the use of combinations of professional skills becomes more important in treatment as the complexities of this increase.

RADIATION THERAPY

Radiation therapy as the initial method in the treatment of localized lymphoma (frequently with curative intent) remains unchallenged. This is emphasized by the encouraging reports of Craver, Peters and Middlemiss, Kaplan, Easson and Russell, and others. The availability of supervoltage radiation therapy at many centers has encouraged the therapist to deliver rela-

tively high dosage to large segmental lymph node groups above and below the diaphragm in Hodgkin's disease. 6, 8,10

I, LOCALIZED (STAGE I-II) MALIGNANT LYMPHOMA

Vigorous radiation therapy of early Hodgkin's disease (when only one or two adjacent groups of lymph nodes appear involved) has produced a significant number of remissions of long duration. By this, we imply the delivery of tissue doses of the order of 3,000 to 4,000 rads. Prophylactic treatment of contiguous groups of lymph nodes in Hodgkin's disease appears worthwhile on the basis of reports by Peters and Middlemiss, 16 Kaplan, Fuller and Fletcher,6 and Karnofsky et al.,10 although statistics based on a large randomized series are lacking. Furthermore, the availability of diagnostic studies such as lymphangingraphy and inferior vena cavagraphy has extended the range of classification and raised new questions regarding treatment.18 It seems reasonable, in the case of Hodgkin's disease at least, to irradiate involved lymph node segments even though this requires extensive treatment of lymphatics above and below the diaphragm. The long term effects of such treatment will have to be observed, particularly as this relates to immune mechanisms and tumor-host relationship. It should be mentioned that the prophylactic treatment of lymph nodes in lymphosarcoma and reticulum cell sarcoma did not appear to yield more favorable results as reported by Peters.14

II. GENERALIZED LYMPHOMA (STAGE III)

A. Lymph Node Disease. Radiation therapy directed to groups of involved lymph nodes (when disease appears limited to the lymph nodes) often provides the most effective method of prolonged control. It is possible to irradiate large segments of

^{*} Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8-10, 1965.

lymphatic tissues if this is done in a sequential manner with careful observation of the blood. Supervoltage is valuable since its use permits higher dosage to involved lymph node groups with a lower integral dose than is possible with lower energy systems.

B. Organ and Parenchymal Disease. When disease is generalized, irradiation of bulky masses is indicated. Localized bone lesions, lesions of the gastrointestinal tract, and localized lung parenchyma can be effectively treated with ionizing radiation. Surgical excision of a solitary lesion of the stomach or intestine may be indicated initially and followed by radiation therapy. Treatment of parenchymal lung lesions should be planned with appropriate verification techniques and dosage limited to perhaps 1,200 to 1,800 rads to avoid pulmonary fibrosis. There is little likelihood of "cure" when lung involvement is apparent, and the use of high dosage is not indicated.

RADIATION THERAPY COMBINED WITH CHEMOTHERAPY

The use of radiation therapy in combination with chemotherapy can provide an immediate therapeutic effect in urgent situations. Prompt administration of a rapidly acting agent provides initial treatment for a patient too ill to be moved. This may occur in cases showing respiratory obstruction, intracranial disease, spinal cord compression, and ureteral obstruction. We believe that combined treatment of superior vena caval obstruction has merit in certain cases; however, it has been shown by Rubin and co-workers that aggressive treatment with radiation alone is effective. 17

Combination therapy can be applied in the face of extensive disease accompanied by systemic signs of toxicity. Thus, prompt control of pyrexia, severe pruritus, night sweats and malaise can be achieved at the same time that symptomatic tumor masses are irradiated. The use of chemotherapy may reduce bulky disease allowing smaller radiation portals to be utilized. This may be particularly valuable in reduction of extensive mediastinal lesions which otherwise would entail irradiation of a large volume of lung parenchyma.

CHEMOTHERAPY ALONE

Treatment of malignant lymphoma by chemotherapy alone may be indicated in certain clinical settings.

I. CONTROL OF SYSTEMIC SYMPTOMS WITHOUT CLINICALLY LOCALIZED DISEASE

The use of a systemic agent is warranted for relief of toxic manifestations of generalized disease. This is particularly important when localized lymph node or parenchymal disease cannot be delineated and irradiated in an individual with an established diagnosis.

II. TREATMENT OF RECURRENT DISEASE IN AREAS PREVIOUSLY IRRADIATED INTENSIVELY

Damage to the lung and respiratory function due to radiation fibrosis can occur after high dosage to large volumes of parenchymal tissue. It is of obvious importance to distinguish between roentgenographic changes due to lymphoma and those secondary to radiation effect. This can be difficult especially if both processes occur synchronously, which is not infrequent. Chemotherapy may be useful in the treatment of recurrent disease involving the lung and other tissues which may be damaged after repeated courses of radiation therapy. Before re-treatment is instituted, consideration must be given to the late effects of irradiation upon the spinal cord, the kidneys, the large and small intestine and to a lesser extent, the brain.

III. THE INTRACAVITARY (OR SYSTEMIC) ADMINIS-TRATION OF A SUITABLE AGENT TO CONTROL ASCITES OR EFFUSION

The instillation of nitrogen mustard and other alkylating agents into the pleural space has been helpful in controlling recurrent effusion due to lymphoma. Quinacrine used intrapleurally and intraperitoneally

has also been reported effective in this situation.²⁰ Thio-Tepa used intraperitoneally has been of benefit in relieving ascites due to these diseases.¹

DISCUSSION

The clinical situations in which chemotherapy is indicated have been discussed. The alkylating agents, mechlorethamine hydrochloride (HN₂, Mustargen), chlorambucil (Leukeran), triethylene thiophosphoramide (Thio-Tepa) and cyclophosphamide (Cytoxan, Endoxan) are the drugs with which there is the greatest experience. They may be indicated when it is necessary or desirable to use a systemic agent. With the exception of chlorambucil, they can be used intravenously. Being polyfunctional alkylating agents, they act in a similar manner and have similar toxicity. In therapeutic dosage, they will cause a moderate depression of the peripheral blood elements; excessive dosage may cause severe marrow depression with leukopenia and thrombocytopenia. Maximum toxicity generally occurs 14-21 days after the last dose of a therapeutic course. Alopecia occurs in about 25-30 per cent of patients receiving cyclophosphamide18 and hemorrhagic cystitis is seen in about 5 per cent of those receiving this medication. 16 HN2 will cause disturbing nausea and vomiting usually not noted with the other alkylating agents.

Over the past 5 to 6 years, the periwinkle derivatives, vinblastine and vincristine, have clearly demonstrated their effectiveness in the treatment of the malignant lymphomas. ^{2,12} Though the mechanism of action is not known, they inhibit mitosis in metaphase. There is no cross resistance with each other or with radiation therapy or with any other oncolytic agent.

Vinblastine (Velban) has been particularly effective in the treatment of Stage III Hodgkin's disease. Toxicity consists of neutropenia, occasionally alopecia, and peripheral neuritis. These occur infrequently with the doses currently used. A weekly or biweekly intravenous injection of

0.1 mg./kg.-0.15 mg./kg. body weight will bring about subjective as well as objective improvement in a large percentage of patients in whom it is used. Vinblastine must be administered at regular intervals to maintain a remission. We have seen remissions of over I year in patients with Stage III Hodgkin's disease who have received maintenance Velban therapy. This has been accomplished without significant toxicity. Vinblastine has been used when a patient has become unresponsive to alkylating agents or when further radiation therapy is not advisable. It can, however, be used in conjunction with either radiation therapy or an alkylating agent.12 Recently, we have initiated therapy in seriously ill patients with Stage III Hodgkin's disease using Velban to quickly bring about subjective improvement and then following with radiation therapy to control residual disease. Since the neutropenia is transient (the leukocyte count usually returning to pretreatment level by 7 to 14 days), vinblastine does not interfere with radiation therapy especially when large portals are to be irradiated. Of importance is the observation that vinblastine may cause thrombocytosis. It can often be used when the platelets are depressed by the disease process. An oral preparation of vinblastine is now being evaluated, but the response does not appear to be as predictable as that obtained with parenteral administration.

Vincristine may be used in the treatment of advanced Hodgkin's disease² but it can result in neurotoxicity paresthesias, areflexia, and ileus. It is more useful in the management of lymphosarcoma and reticulum cell sarcoma than is vinblastine and at the present time it is infrequently used in the treatment of Hodgkin's disease. Neutropenia secondary to vincristine administration is not likely to occur if the drug is given once weekly in a dose of 0.01–0.03 mg./kg. body weight. It, too, can be used with radiation therapy. Continued use of vincristine is necessary to maintain a remission.

Methylhydrazine is another chemotherapeutic agent useful in the treatment of the malignant lymphomas and especially in Hodgkin's disease.8 The mode of action of this compound has not been completely elucidated. It may prolong the cellular interphase and bring about singular chromosomal alterations. It has also been demonstrated to degrade DNA by the formation of hydrogen peroxides and, therefore, its effect has been compared to that of ionizing radiation. Brunner and Young's reported significant regression of tumor masses and clinical improvement lasting at least I month in 12 of 20 patients with Hodgkin's disease, in 1 of 2 patients with lymphosarcoma and in 1 of 4 patients with reticulum cell sarcoma. The drug induced objective regression of tumor masses in most patients with Hodgkin's disease but therapeutically useful responses were seen only in early cases (with little or no previous therapy) or in patients who were not seriously ill. Therapeutic results were obtained in patients who previously were treated with radiation therapy, alkylating agents and plant alkaloids. When the drug was administered daily in divided doses, therapeutic responses without significant toxicity could be achieved in some patients with Hodgkin's disease by giving 25 to 30 mg./kg./ week for 3 weeks and then reducing the dose to 5 mg./kg./week for maintenance.

Allopurinol (4-hydroxypyrazolo [3,4-d] pyrimidine), or HPP, is a purine base analog which will inhibit xanthine oxidase, the enzyme responsible for the oxidation of hypoxanthine to xanthine to uric acid. Allopurinol will cause the serum uric acid to fall rapidly in patients with gout as well as in patients with malignant lymphoma. In the past, a significant elevation of uric acid delayed the initiation of effective therapy. With this agent, intensive therapy can be instituted within 48 to 72 hours. Allopurinol is given orally, in 100 mg. tablets, in doses of 100-200 mg. 3 to 4 times daily. The administration of large quantities of fluids to ensure a large urine volume is necessary. Toxicity from this agent appears to be minimal.¹¹

SUMMARY

Despite the increasing availability of new and useful chemotherapeutic agents, it should be restated that the primary treatment for localized malignant lymphoma is radiation therapy. When disease is more advanced, experience has suggested broad guide lines favoring radiation therapy alone, combined therapy, or chemotherapy alone in the treatment of certain clinical settings. The need for teamwork in patient evaluation and treatment and future continued investigation is paramount.

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HYBAROXIC RADIOTHERAPY: SOME OBSERVATIONS IN THE DEVELOPMENT OF CLINICAL APPLICATION AND TECHNIQUE*

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HE oxygen effect in radiobiology is ubiquitous. Furthermore, it is quantitatively as constant as anything in biology. Its effect extends beyond biology into the area of inorganic radiation reactions. Reference to these data has been made elsewhere,10 and will not be reiterated. Let it suffice to observe here that to ignore the oxygen state in any radiation-induced reaction is to complicate the observable results by considering a measurable perimeter as an uncontrollable variable. But the transition of the observed oxygen effect from radiobiology in the laboratory to practical daily radiation therapy is complicated by other biologic phenomena far less easily controlled, measured or even described.

Guided by many unspecified laboratory data and much clinical experience, both current and recorded, the step into hybaroxic radiotherapy was taken at the Tumor Institute of The Swedish Hospital in January of 1963. Due to our particular status in the community, the application needed to be a practical one. It also needed to improve the art of radiotherapy in such mundane perimeters as patient tolerance as well as local control of cancer at higher rates in familiar problems. Hopefully, it might extend the application of radiation therapy to new areas in cancer control. It might even increase the cure rate beyond the sense as lately applied to results in Hodgkin's disease.8,6

It had been our intent in the beginning of our study of hybaroxic radiotherapy to extend the radiation dose program of Churchill-Davidson and Van Den Brenk away from survival-curve type data toward more conventional programs, steering a

course that would take advantage of both approaches. 2,8 In order to stay within the realm of reasonable economics, it was desirable to make some time-dose adjustments to afford the added expense of hybaroxia within the practical economics of private hospital radiotherapy. It should be emphasized here, however, that we were persuaded that even direct application of the British and Australian experiences would make the technique an acceptable addition to the armamentarium of the radiotherapist.

During the first 2 years of our experience with hybaroxia, we completed 3,766 patient cycles from atmospheric pressure to 30 pounds per square inch pressure and back to normal again, in 100 per cent oxygen. More than 456 different people were subjected to the procedure (Table 1). From this experience we observed that the procedure can be done on outpatients of all ages, without premedication. Coaching is necessary as to methods of decompressing the middle ear and uses of the communication system of the machine to minimize the sense of isolation. No routine surgical preparations are required, but complications such as long-standing, chronic otitis media or acute upper respiratory infections may make decongestants advisable and even myringotomy useful at times.

The hyperbaric vessel must be as unimposing as possible, and mechanically capable of gentle regulation of pressure changes to allay apprehension and outright discomfort. By avoiding anesthesia, there are many advantages. The patient's actual treatment position is determined prior to his being placed in the machine. He can then relax and adjust to the changes in at-

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TABLE I
TOTAL HYBAROXIA EXPERIENCE

Hybaroxic Radiotherapy	341
Hybaroxia Only	341 60
Interrupted Treatment	12
Intolerance	6
Volunteers	37
Total People Exposed Total Exposures	456 3,766
<u>-</u>	

mospheric pressure in his most comfortable position. Then after reaching full pressure, all the usual methods of instruction to the patient for positioning can be carried out, except touching him. No complicated headholders are required. Above all, when the treatment is over, the patient can dress and return to his normal activities. In the case of the anesthetized patient, a day of sleep usually follows the treatment because of the depository type of anesthesia that must be employed for the isolated patient.

Large transparent windows or totally transparent walls of the chamber reduce the sense of confinement and, except in pathologic claustrophobia, vield good acceptance. The audio and voice contact with the attendant on the outside also reduces the sense of isolation. The flow-type chamber has the advantage of making 100 per cent oxygen available to the patient. No contamination of oxygen can be measured at the exhaust by Beckman oxyometer by the time the patient has reached the first 3 to 4 pounds of pressure. With the closed-off system, after a flushing of the chamber and patient, the exhaust is closed and the machine is charged with oxygen. A carbon dioxide contamination as high as 5 mm. Hg has been measured by the end of treatment.9

Hybaroxic equipment in the department will lead one into many fields of exploration beyond radiotherapy. Table II indicates some of our interests developing in this line. The value of this may be pointed out by the observation that it is with these patients that we have seen the

prodromal signs of impending "oxygen intoxication." The symptoms occurred in patients with fever, patients who were toxic, and in diabetics with high blood sugar. The only convulsion in hybaroxia we have seen occurred in this group of patients. We were using hybaroxia for control of an anaerobic diplococcus osteomyelitis of the upper femur complicating the removal of a pin after an unsuccessful open reduction of a fracture. She had been a patient at the Artificial Kidney Center for 2 years. Because of the duration of the hybaroxia and the character of the convulsion—particularly as to lack of prodromal symptoms and because these people without kidney are subject to convulsions especially at the time of dialysis, shifts in body chemistry were probably more important in the genesis of the seizure than hyperbaric oxygen. These studies were helpful as guidelines to the status of patients acceptable for hybaroxic radiotherapy.

From the above, we observed that hyperbaric oxygen to 30 pounds per square inch gauge pressure can be tolerated at all ages, without anesthesia, with fewer complications than the alleged radiation-potentiating drugs under study at this time.

The coupling of the procedure "hybaroxia" to radiation therapy in order to obtain the advantage of treating all tumor cells without the protective influence of anoxia, poses new problems as well as solving the original. How does one determine that anoxia has been eliminated? No oxygen-measuring instrument has been developed that is sensitive to diameters equiv-

TABLE II

NONRADIATION HYBAROXIA

Ischemic Gangrene	22
Arterial Occlusion	9
Acute Anuria	6
Gas Gangrene	7
Mixed Infections	16
	_
Total	60

alent to the known maximum diffusion of oxygen through living cell masses under normal physiologic conditions. Measurement of the venous oxygen partial pressure, such as in the antecubital vein, is practical and reasonably innocuous. Can one legitimately allege that the partial pressures of oxygen in all capillary beds are no lower? Radioisotopic localization of tumor, intraarterial opacification of tumor-bearing areas and infrared thermography depend on puddling of test material in the abnormal vascularity of the tumor. What assurance is there that the hybaroxic-charged blood flows through these blood sinks with normal circulation time? Or are these important considerations? Histologic studies, both personal and reported, show that beyond a maximum of 200 μ distance from the stromal blood supply, the tumor mass is anoxic and necrotic. 7,10 The thickness of the living cancer cell mass averages 150 μ , the same as for normal cells dependent upon normal vascular components. It follows, then, that the tissue PO2 must respond to changes in vascular oxygen tensions in the same fashion and rate in cancer as in normal living cells. While 30 minutes may be required for oxygen equilibrium to be reached at the site of a polarographic probe in a gross tumor mass, each living fragment of that tumor mass, capable of mitosis, is within 150 μ of a source of oxygen. Only diffusion over such diameters is important. All else is dead and inconsequential.

Observe, then, that the time for diffusion of oxygen through 150 μ of living cells determines the rate at which protective anoxia disappears with hybaroxia. With the volume of oxygen dissolved at 30 pounds per square inch, doubled from a normal of 6 to 12 volumes per cent, and the partial pressure increased from 40 mm. Hg in the venous blood to 1,600 mm. Hg, the 150 μ diffusion must be accomplished by the time the measurements in the antecubital vein have been read and recorded.

Radiation dosage poses no less problem in hybaroxia than in air. Because of the

equipment used in early studies and the resultant need for anesthesia, a simplified dosimetry was required. Van Den Brenk and co-workers related their dose schemes to the survivalcurve, and on a two- or threeincrement pattern used single dosages that would yield a survival of somewhere between 10⁻⁷ and 10⁻¹⁰ cells.8 Since the response to such dosage is proportional in all tissues, tumor or normal, for any end-point studied, and since at this dosage range recovery can be ignored, mass tissue death without reactive repair attempts is expected and observed. Even at our original schedule of 600 rads repeated dosage for 6 sessions, reactive cell infiltration and capillary budding were largely eliminated.

It is then possible to observe that the marked increase of mucous membrane reaction and tumor tissue necrosis reported in hybaroxic radiotherapy is more dose-dependent than a function of the elimination of anoxic cancer cells by hybaroxia or increased radiation sensitivity of normal tissues.8

At the other end of the scale lies the experience of Johnson⁵ and associates at the Manitoba Cancer Foundation of Winnipeg, who added hybaroxia to their previously tested radiotherapy schedule for treating Stage III and Stage IV cancer of the cervix— 5,000 to 6,000 rads in 6 to 7 weeks. But such a schedule of hybaroxic radiotherapy is long, arduous and expensive. It cannot be funded by the present medical insurance programs. Can an abbreviated schedule be developed without loss of normal tissue preservation—the basis for orthodox radiotherapy schedules? In these conventional high-total-dose schedules, the daily increments are less than the dose derived from the logarithmic portion of the survival curve for mammalian cells—about 300 rads. In our hybaroxic radiotherapy for a multiplicity of reasons, a similar dosage schedule has been used in cancer of the esophagus and in any tumor situation wherein multiple portals are necessary to deliver the deep tumor dose. Since stromal

TABLE III
HYBAROXIC RADIOTHERAPY

Skin and Adnexa	19
Intraoral	48
Upper Air and Food Tract	6 8
Lung and Bronchus	24
Esophagus	25
Abdominal Digestive Organs	36
Genitourinary	13
Musculoskeletal	23
Lymphomas	27
Lymph Node Metastases	52
Central Nervous System	6
·	
Total	34I

reaction was present and cancer regression successful, our second series dosage was 300 rad tumor dose increments to a total of 3,600 rads. In the oral cavity this reduced the mucosal reaction from confluent mucositis to a patchy one, and the tumor resolution continued as satisfactorily except in cancer of the oral tongue. At our present developmental stage of the art, we find that for fields covering most of the oral cavity, the nasopharynx, the tonsil, base of tongue, palate, oropharynx, epiglottis and vallecula and the lymphatic drainage of these structures, or the laryngeal apparatus, a daily tumor dose of 250 rads × 16 is an acceptable schedule worthy of exploration. In the lung and esophagus, 3∞ rads \times 12 seems to be equally acceptable as long as one avoids any larger dose in vital, sensitive interposed structures.

The oral tongue, as usual, seems to be a special problem. We have observed complete resolution of fixed cervical lymph node metastases with 3,600 rads in 12 increments, but persistence of a rapidly recurring cancer in the primary site in the tongue. It is our present plan to deliver 2,000 rads in 8 increments. If there is rapid change in the appearance of the tumornecrosis, shrinkage and slough—a 2 week break in treatment is allowed for elimination of the dead tumor tissue and recovery of the stroma and vascular structures in the field of radiation. When mucosal reac-

tion has subsided, a second schedule similar to the above is delivered, and guided in time by continuous observation. However, if little change occurs within the original series, hybaroxic radiotherapy should be slowed in daily dosage and continued without break, or the method abandoned in favor of radium implantation for total tissue destruction or extirpative surgery.

From the explorations indicated in Table III, certain observations seem appropriate at this juncture:

- 1. When a major salivary gland is in the field of radiation, doses as low as 200 rads may result in massive swelling within 6 to 24 hours. The swelling is usually associated with eating, resolves spontaneously, and seldom recurs.
- 2. Relatively ischemic and normally avascular tissues such as cartilage, cornea and perhaps cortical bone, demonstrate an increased radiation response in hybaroxia. On the basis of this, Howard-Flanders and Wright⁴ were able to calculate the oxygen partial pressures of the epiphyseal plates of the tails of immature rats. In every instance where we have treated cancer with a cornea in the field of radiation, destruction of the latter has occurred within 3 months with doses of 3,000 to 4,000 rads.
- 3. The spinal cord deserves a special word of warning. Acute, tingling paresthesias invariably appeared, if sought for, when the cervical spinal cord was irradiated with 3,500 rads. The latent period was shortened by 2 to 4 months over that seen with conventional radiation programs. In the dorsal cord, no early reactions have been recorded, but at I year to 15 months, true symptoms of demyelinating disease, with foot drop and a Brown-Sequard syndrome, appeared. Another patient treated for cancer of the lower esophagus proceeded to paraplegia by the time she succumbed. From our present experience with hybaroxic radiation of the thoracic esophageal cancer, the survival period has been increased in many more patients than was our experience with conventional radiation therapy. Perhaps the reason a thoracic

cord radiation myelitis was so rarely observed previously is that relatively few patients with cancers arising in the thoracic area survived long enough to experience it. Precautions must be taken to protect the thoracic cord.

- 4. Well differentiated adenocarcinoma, such as from the gastrointestinal tract, rarely shows a growth pattern of central necrosis. Its response to hybaroxic radiation has been disappointing, in the primary sites, lymph nodes, and in liver metastasis. On the other hand, undifferentiated adenocarcinomas, especially pancreatic metastases in lung, mediastinum or supraclavicular lymph nodes, seem to be in the same response category as squamous cell carcinoma.
- 5. The response of metastatic cancer of the pancreas to radiation led us to accept patients found to be nonresectable at laparotomy. The results have been disappointing. Only in those rare instances in which an enlarged "C" loop is seen on roentgenograms and observed to regress with hybaroxic radiotherapy has there been any demonstrable reward for the effort.
- 6. We looked for patients with metastatic malignant melanoma because of the reported paramagnetic behavior of melanin in electron-spin resonance studies.¹⁰ While the response has been better than we have ordinarily come to expect with radiation therapy of melanomas, there have been too many instances of failure to make hybaroxic radiotherapy the treatment of choice for the first attack in resectable situations, but it is still worthy of further study.
- 7. At this juncture in our study of hybar-oxic radiotherapy, we believe it justified to issue a word of warning to therapists who study this modality in the treatment of patients with advanced cancer with known or unknown areas of widespread metastasis. Areas of cancer beyond the field of radiation seem to grow with alacrity. The full course of the disease seems shortened, and areas of metastasis seem to grow to a much larger size than ordinarily seen. Admit-

tedly, the outcome is unchanged and much can be learned from the response of cancers to this form of radiotherapy. But liver metastasis of unusual size, magnified disemination of disease, rare sites of spread and a shortened prognosis for survival seem apparent and require consideration.

SUMMARY

Above all else, the radiotherapist must never ignore the axiom that hybaroxia protects no tissue; it is merely a method of restoring a lost radiation sensitivity to the anoxic portions of a cancer cell mass. Only when such pertains can it be of any value in the treatment of cancer by radiation therapy. Hyperbaric oxygen gives no license to violate radiotherapeutic truths learned through the experience of conventional methods. However, in that large and important group of cancers that respond well and early to modest doses of radiation but require high doses to cure, one has reason to expect that all of the cancer cells will respond to the lower total dose when irradiated in high pressure oxygen. From nonradiologic hybaroxia patients, one observes the general metabolic support, bacterial suppression, toxin oxidation and improved patient tolerance that make radiation therapy of cancer less of an ordeal for the patient when supplemented with this modal-

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OXYGEN EFFECT FACTOR AND TUMOR VOLUME IN THE C.H MOUSE MAMMARY CARCINOMA

A PRELIMINARY REPORT

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MOLECULAR oxygen is a highly potent sensitizer of mammalian cells to the lethal effects of x and gamma irradiation. This has been shown by the experimentally determined ratios of D₂₇ values (cellular radiosensitivity) of anoxic to aerobic cells which have been in the range of 2.3-3.0.3 Importantly, the increase of radiosensitivity with increase of oxygen tension occurs almost entirely in the range of 0-10 mm. Hg tension. These facts are relevant to the interests of clinical radiotherapy because oxygen is normally present in the body fluids and tissues. This is especially pertinent since oxygen is nearly maximally sensitizing at the physiologic concentration of oxygen in most normal tissues, but the oxygen tension in some viable tumor cells may be extremely low, i.e., essentially zero. The role played by these oxygen tension differentials between cells of normal and malignant tissue in determining the probability of success of radiotherapy in achieving local control of tumor has been discussed recently in detail in several excellent reviews.2,8,4

We wish to present a preliminary report of results from animal tumor experiments which were planned to determine the effect of tumor volume on radiation dose-tumor control response curves for air breathing animals. In addition, we have determined the effect on such curves: (1) exposing the animal to 100 per cent oxygen at 4 atmospheres pressure absolute for 15 minutes prior to and then during the irradiation, and (2) rendering the tumor and surround-

ing normal tissues anoxic at the time of irradiation.

MATERIALS AND METHOD EXPERIMENTAL ANIMAL TUMOR SYSTEM

Weanling female mice of the inbred C₁H mice were supplied by the Roscoe B. Jackson Memorial Laboratories, Bar Harbor, Maine. From the same source, an adult female mouse of the same strain of mice (mammary tumor agent positive) that carried a single spontaneous mammary carcinoma was obtained. All experiments described in this report have been based on second to fourth generation isotransplants derived from a single mammary carcinoma. Details of preparation of cell suspension, tumor cell transplantation, measuring tumor volume, scoring of recurrences, and statistical analysis of local control results have been previously described. A complete description of the x-irradiation facility has been given previously.5

POSITIONING OF MOUSE AND TUMOR FOR IRRADIATION

Anesthesia for these animals was achieved by an intraperitoneal injection of 0.07 mg. nembutal per gram of mouse. Following induction of anesthesia, the mouse was taped to a simple brass tray so that the tumor bearing part was positioned over the cut-out, *i.e.*, that part of the tray which would be covered by the field of irradiation after the tray had been locked into position in the x-ray facility. For the

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air and high pressure oxygen irradiation, there was no known interference in the blood supply to the tumor bearing part. In the tumors treated under anoxic conditions, the brass clamp fitted to the tray not only occluded the blood supply to the part to be irradiated but fixed the tumor in position for treatment. All radiation doses are given in terms of the dose in rads in the central portion of the tumor.

PRODUCTION OF ANOXIA

A circular brass clamp was fitted across the base of the ear or uppermost portion of the thigh and maintained for ≥ 1 minute prior to the initiation of the irradiation. As an additional precaution during irradiation, oxygen in the air surrounding the part being irradiated was displaced by a stream of nitrogen passing from above and below. The resultant O₂ concentration in the immediate environment of the irradiated part was less than 1 per cent, as determined by measurements with a miniaturized Clark electrode.

HIGH PRESSURE OXYGEN CHAMBERS

Special brass chambers were obtained* so as to irradiate locally the mouse tumors while the animals were exposed to 44 psi (4 atmospheres pressure absolute) of 100 per cent oxygen. The chambers were positioned in the x-ray facility so that the tumor bearing part was in the central portion of the treatment field (confirmed by localization films). The chamber was flushed with oxygen and then pressure increased at a rate of 12 psi per minute to a final level of 44 psi. This pressure was maintained for a minimum of 15 minutes and then the irradiation was started. During the period at this level of pressure, an oxygen flow rate of 4 liters/min. was maintained (volume of chamber with I mouse inside is 290 ml.). At completion of treatment, pressurization was decreased over a period of I minute. Animals were pinkish in color at completion of such a procedure. However, the 250 mm.³ tumors remained dark bluish in color, *i.e.*, they were not grossly altered by the exposure to oxygen. The radiation dose rate inside these pressure chambers was 0.344 the dose rate used for air and anoxic irradiation.

EXPERIMENTAL GROUPS

Groups of 150-240 sequentially numbered animals were placed by use of a random number table into one of 5 to 10 dose groups in each of the three dose response curve studies at a given tumor volume. A total of 802 animals has been used in these experiments. Two such sets of experiments were performed on tumors of 8 mm. diameter in the thigh, and one set of experiments each at I mm. diameter growing in the ear and at 72 hours following injection of 105 cells into the thigh muscle. During the time that the tumor volumes were approaching the volume at which they were to be irradiated, the three diameters of the tumor were measured daily in order that all of the tumors in a dose response study were irradiated at the same volume. Thus, the tumors in any one dose response curve were irradiated over a period of 2 to 4 weeks. This contrasts with the last experiment, in which all animals were irradiated at 72 hours after tumor cell transplantation.

RESULTS

Radiation dose response curves using local control of tumor as the end point are presented in Figures 1, 2, and 3 for the transplanted mammary carcinoma of the C₃H mouse at 250 mm.³, 0.6 mm.³, and ≈ and 0.001 mm.³ volumes. These curves are logit regression lines that have been fitted to the 90 day or 60 day local control results. At each tumor volume, three dose response curves are shown which are based on tumor irradiation for different conditions of tissue oxygen tension: (A) animals breathing 100 per cent O₂ at 4 atmospheres pressure absolute (O₂ 44 psi) for 15

^{*} These were designed and constructed by Mr. B. Moore in the Engineering Section, Department of Physics, M. D. Anderson Hospital, Houston, Texas.

minutes prior to and then during irradiation, (B) animals breathing air at I atmosphere of pressure, and (C) local tissue anoxia.

TUMOR TRANSPLANT TAKE RATE

The tumor transplant take rate varied between 92 and 100 per cent for the experiments using 250 mm.³ and 0.6 mm.³ volume tumors. In the experiment where irradiation was given 72 hours after injection of tumor cells, tumor developed in 18/18 of the control animals.

250 mm.³ Tumor. The curves as shown in Figure 1 are logit regression lines fitted to the pooled data from two complete and essentially identical experiments. The TCD_{50/90 days}, values for a given condition of irradiation were not different, *i.e.*, P>0.05 in the two experiments.

For these large tumors, which were characterized by the presence of grossly

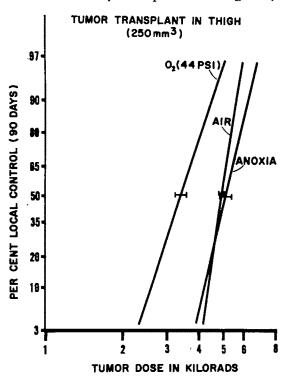


Fig. 1. Tumor control incidence at 90 days after irradiation of 250 mm. tumors growing in the mouse thigh. Brackets indicate the standard error of the TCD₁₀ estimate.

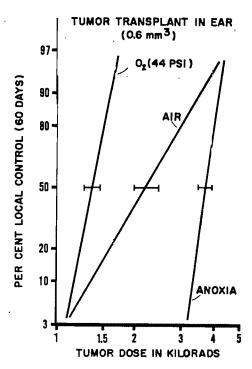


Fig. 2. Tumor control incidence at 60 days after irradiation of 0.6 mm.³ tumors in the mouse ear. Brackets indicate the standard error of the TCD₅₀ estimate.

necrotic areas and cystic blood filled regions, the "air" dose response curves did not differ from that obtained when the tumor and surrounding normal tissues were rendered anoxic. However, exposure to 100 per cent O₂ at 44 psi for 15 minutes was effective in sharply displacing the curve to the left. The TCD₅₀ of 3,490 rads for curve A was significantly less than the TCD₅₀ of 5,020 rads for curve B (P<0.05). In Table 1 are listed the ratios of

TCD₅₀ Anoxia

and

TCD50 Anoxia TCD50O2 44 psi

for the three tumor volumes studied. For the 250 mm. volume, the ratio of 1.5 for

TCD₅₀ Anoxia TCD₅₀O₂ 44 psi

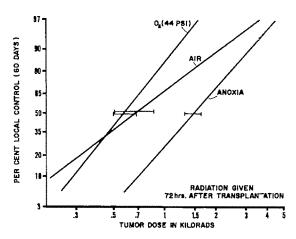


Fig. 3. Tumor control incidence at 60 days after irradiation of thigh that had been injected with 105 "viable" tumor cells at 72 hours prior to irradiation. Brackets indicate the standard error of the TCD₅₀ estimate.

was less than the ratio of 2.3-3.0 which would have been obtained if all of the tumor cells had been made aerobic by the exposure to 100 per cent O₂ at 44 psi.

0.6 mm. Tumor. In this experiment, the curve for tumors in air breathing animals was in the mid-position between the O2 44 psi and the anoxia curves, and it was much less steep. This indicates that some of the tumors under normal conditions were composed almost entirely of aerobic cells while the remaining tumors had variable proportions of aerobic and hypoxic cells. If these tumors had had a constant fraction of cells that were anoxic, i.e., 10-2 or 10-3, the dose response curve would have been parallel to curve C but displaced to the left by a distance reflecting the size of the fraction of cells that were anoxic. That curve A was parallel to curve C and the ratio of

TCD₅₀ Anoxia TCD₅₀O_{2 44} psi

was 2.8 indicates that exposure of the animal to 100 per cent O₂ at 44 psi for 15 minutes was effective in raising the O₂ tension to aerobic levels in essentially all of the tumor cells in all of these small tumors.

TUMOR CELLS IRRADIATED 72 HOURS AFTER TRANSPLANTATION

In this experiment 100,000 "viable" cells, as determined by count of tumor cells that failed to stain with trypan blue, were injected in a volume of 5 µl. into the thigh muscle. Irradiation was given 72 hours later, when the cells that had survived would have been expected to have started proliferation and have established small "clones" of cells. Presumably, such cells would have had an oxygen tension corresponding to that of the surrounding normal tissue cells. As seen in Figure 3, the "air" and "O₂ 44 psi" curves were very close at the TCD₅₀ point, but again the "air" curve was less steep. The ratio of

was 2.6 or similar to that observed for the 0.6 mm.⁸ tumors.

That the curves A and C for these very small tumors were much less steep than for those in Figure 1 and 2 was almost certainly due to the fact that the radiation was given at a fixed time after transplantation, i.e., there would have been considerable variation in the number of viable tumor cells. This contrasts with the other experiments where radiation was given to a tumor of a specified volume, i.e., the time of irradiation after transplantation varied.

The viable tumor cells present in the thigh at the time of irradiation were estimated to have represented a volume of 10-3mm.3. It is assumed that a very large fraction of the

Table I

OXYGEN EFFECT FACTOR AND TUMOR VOLUME

Tumor	TCD ₅₀ Anoxia	TCD ₆₀ Anoxia
Volume	TCD ₅₀ Air	TCD ₆₀ O ₂ 44 psi
250 mm.³	I.O	1.5
0.6 mm.³	I.7	2.8
≈.∞1 mm.³	2.2	2.6

tumor cells did not survive long enough to establish a clone of tumor cells in the muscle. The TCD_{50} (anoxia) at 60 days of 1,512 rads would be expected to increase to a TCD_{50} at 180 days of \approx 2,000 rads as additional recurrences are scored. Such a TCD_{50} for anoxic cells of the C_2H mouse mammary carcinoma would be expected to correspond to that which would be obtained for treatment of a tumor \approx 5.10⁻⁴ to 10⁻³ mm.⁸ or a tumor composed of 500 to 1,000 viable cells. This assumes a D_{37} of 300 to 325 rads and N=1-6 and that one or more cells surviving the irradiation would produce a recurrence.⁶

DISCUSSION AND SUMMARY

These results are preliminary in that they are based on 60 day and 90 day tumor control rates. The TCD₅₀ values will increase as observation times are extended to 150–180 days. However, neither the slopes of the dose response curves nor the ratios of

TCD₅₀ Anoxia TCD₅₀O₂ 44 psi

would be expected to change with the increase in the absolute TCD₅₀ values.

Although these results must be classed as preliminary, they do demonstrate three findings. Firstly, in the large mouse mammary carcinoma which had grossly necrotic areas, the dose response curve for the "air" irradiation was similar to that for anoxic irradiation. Secondly, even though the TCD₅₀ for such tumors in animals exposed to 100 per cent O₂ at 44 psi was significantly less than for "anoxic" irradiation, the ratio of

TCD₅₀ Anoxia TCD₅₀O₂ 44 psi

was only 1.5, i.e., less than the value of 2.3-3.0 that would have been observed had the oxygen tension in all of the cells of the O₂ 44 psi treated tumors been increased to aerobic levels. Thus this oxygen therapy

was not effective in increasing the oxygen tension to aerobic levels in all regions of the tumor. Thirdly, the dose response curve for the tumors of I mm. diameter, when irradiated at normal conditions, indicated that there were at least a few anoxic or severely hypoxic cells in most of even these quite small tumors. However, for these tumors and the even smaller ones (Fig. 3), the oxygen tension of all tumor cells was increased to aerobic levels by the oxygen treatment used (as estimated by the radiobiologic response). That is, in this animal tumor system exposure of the animal to high pressure oxygen was quite effective for the really small tumors and of an intermediate effectiveness for the tumor containing grossly necrotic areas.

These results are similar to the findings of Belli and Andrews¹ that the proportion of anoxic cells present in the P388 lymphoma cells growing in the peritoneal cavity in the ascitic form increased from ≈ 0 to nearly 100 per cent by the seventh day of tumor growth.

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EFFECT OF FOCAL IRRADIATION ON HUMAN BONE MARROW*

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SINCE the initial animal studies by Heineke in 1904,¹⁰ a vast literature has accumulated concerning the effects of irradiation on hematopoiesis. Emphasis continues to center on studies of total body irradiation. Relatively little information exists regarding specific qualitative and quantitative changes of bone marrow during human partial body therapeutic irradiation.^{8,5,9,11,15,20,21}

We have observed the acute effect on hematopoiesis during partial body irradiation by serial morphologic studies of marrow from irradiated and nonirradiated sites during the initial course of therapeutic irradiation in 9 patients with cancer of the breast, lung, or esophagus.

MATERIALS AND METHODS

Teletherapy with 250 kvp. (half value layer 1.5 mm. copper), Co⁶⁰, or 6 mev. (linear accelerator) was administered as outlined in Table 1. None of the patients had previous irradiation or chemotherapy, and no chemotherapy was administered during the study. Patients with known marrow metastasis were excluded from the study, but in 1 patient, tumor cells eventually were proved at a single site of marrow aspiration.

With the use of the University of Illinois or the Vim-Silverman needle, paired marrow aspirations were made from the sternum and iliac crest, one site being in the field of irradiation. The sites of local aspiration were varied to avoid dilutional effects of repeated aspirations. Aspirations were made prior to therapy and, when possible, after marrow doses calculated to be approximately 400 r in 3 days, 1,000 r in 8 days, and 2,000 r in 16 days. The marrow

dose for each aspirate was calculated at a tissue depth of 3 cm. from standard-depth dose curves. The calculations did not take into consideration the shielding effect of bone for each energy source. Marrow aspirates were expelled into plastic vials containing five drops of a 10 per cent solution of sequestrene Na₂. Smears of marrow were stained with Wright's stain, and 500 nucleated cells were classified. A portion of the aspirate was placed in a Wintrobe hematocrit tube and centrifuged at 2,000 r.p.m. for 5 minutes, and the height of the buffy coat or myeloid-erythroid (ME) layer was determined. This value was used to calculate the absolute index for each stage of cellular development. The absolute index, a semiquantitative expression, is the product of the volumetric ME value and the relative percentage of each cell type. 18 The reliability of the ME value as a measure of marrow cellularity is disputed, but the ME value is generally considered to have merit in interpreting differences between group samples. 1,14 The normal value of the ME layer is 4 to 8 mm.

The remaining portion of the marrow aspirate was filtered to separate the marrow particles, which were fixed overnight in a 4 per cent solution of formalin (in 0.9 per cent saline), embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

The hemoglobin concentration, as well as erythrocyte, reticulocyte, leukocyte, differential, and platelet counts were determined at the time of each marrow aspiration.

RESULTS

Irradiated Marrow. Prior to irradiation, the cellularity and differential cell counts

* Mayo Clinic and Mayo Foundation: From the sections of medicine (Dr. Kiely), clinical pathology (Dr. Pease), and therapeutic radiology (Dr. Scanlon). Dr. Lehar is a resident in medicine, Mayo Graduate School of Medicine (University of Minnesota), Rochester.

 $T_{\tt ABLE}\ I$ description and radiation data in 9 patients receiving focal irradiation of bone marrow

Age (yr.) and	Diagnosis	Fields, No., and	Energy	Aspirated Marrow Dose (3 cm. depth) (r/days)		
Sex		Size (cm.)*		400 r	1,∞∞ r	2,000 r
61, F	Adenocarcinoma, breast (grade 4)	8 by 15	250 kvp.	470/4	940/8	
70, M	Squamous carcinoma, esophagus (grade 4)	2 opposing 9 by 20	6 mev.		1,035/8	2,300/17
77, F	Adenocarcinoma, breast (grade 3)	8 by 15	250 kvp.		1,050/7	
65, M	Small cell carcinoma, lung	2 opposing 14 by 26	Co60	530/3	912/6	1,750/12
52, F	Adenocarcinoma, breast (grade 3)	1 8 by 15	250 kvp.	340/3	1,040/8	
47, F	Adenocarcinoma, breast (grade 4)	8 by 15	250 kvp.	***************************************	1,220/8	1,900/13
71, M	Pubic ramus metastatic adeno- carcinoma, breast (grade 3)	2 16 by 18	Co ⁶⁰	APPROXIMAL APPROXIMATION APPRO	1,175/8	
34, F	Adenocarcinoma, breast (grade 4)	8 by 15	250 kvp.	*******	1,040/7	2,080/15
70, F	Adenocarcinoma, breast (grade 3)	1 8 by 15	Co ⁶⁰	- Miles	1,260/8	1,920/15

^{*} Irradiated area: sternum in all but I patient (71 year old man).

from the paired aspiration sites were similar. After 3 days $(4\infty \text{ r})$, little change in cellularity was apparent in the irradiated marrows; but, after 8 days of therapy $(1,\infty)$, the marrow cellularity was reduced to approximately 40 per cent of normal; and, on the sixteenth day $(2,\infty)$, it was reduced to 20 per cent of original cellularity as estimated by study of tissue section (Fig. 1, a-d) and determined by the absolute index (Fig. 2a).

The relative percentage of normoblasts decreased markedly after 3 days (400 r), with a relative persistence of the polychromatophilic and orthochromatic forms (Fig. 3a). In 1 case, the normoblasts demonstrated many abnormal mitotic figures with internuclear bridging and interphase cells with nuclear particles. Erythroid precur-

sors were absent by the eighth day of therapy.

The reduction in early granulocytes (myeloblasts, progranulocytes, myelocytes) after 3 days was not as marked as it was for normoblasts, but these early forms were practically absent by the eighth day (Fig. 3b). Giant myelocytes and metamyelocytes were a striking feature of early samples, and subsequent aspirations demonstrated maturation of these elements to macropolycytes. Mature granulocytes were persistent, as were mature basophils and eosinophils.

The absolute indices for mononuclear cells were steady during the course of irradiation, although their relative percentages increased (Fig. 3, c and d). Interestingly, foci of lymphocytes were persistent, al-

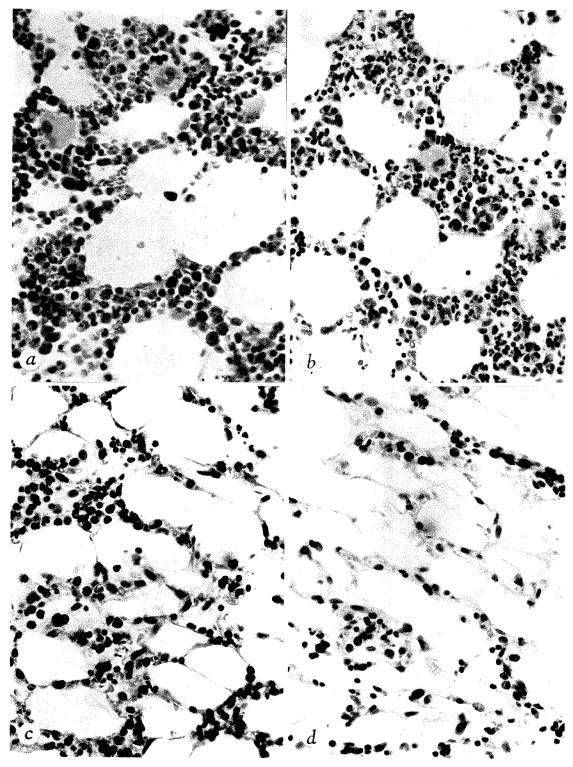


Fig. 1. Irradiated marrow tissue sections demonstrating progressive reduction in cellularity with persistence of plasma cells, lymphocytes, mature neutrophils, and reticular elements. (a) Prior to irradiation. (b) After 530 r in 3 days. (c) After 1,175 r in 8 days. (d) After 1,920 r in 15 days (hematoxylin and eosin; $\times 400$).

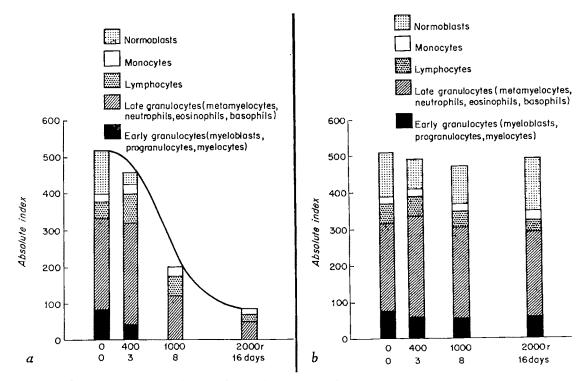


Fig. 2. Marrow cellularity using the absolute indices for each marrow component. (a) Irradiated.

(b) Nonirradiated.

though germinal centers apparently disappeared (Fig. 4b). Nuclear and cytoplasmic vacuolation was apparent in monocytes after 400 r.

Few megakaryocytes persisted after 8 days (1,000 r) and none after 16 days (2,000 r). Plasma cells were radioresistant as demonstrated in marrow particle sections during the course of irradiation and in some cases appeared to comprise nearly 30 per cent of the nucleated marrow cells (Fig. 1, c and d). The differential counts of unconcentrated marrow smears, however, did not reflect the radioresistance of the plasma cell noted on histologic sections. Fat cells and other reticular cells also were persistent although there was no evidence of overgrowth by these elements. Volumetric studies did not demonstrate an increasing fat content.

Nonirradiated Marrow. No significant alterations occurred in the nonirradiated marrows (Fig. 1a and 2b).

Peripheral Blood. The mean leukocyte

count in 6 cases decreased from the pretreatment level of 7,800 cells per cubic millimeter to 5,100 cells. Both lymphocytic and granulocytic mean cell counts decreased. No morphologic changes were apparent in the circulating nucleated cells. Some slight reduction in platelet counts occurred in the latter half of the therapy program, but in no case did significant thrombocytopenia occur (Fig. 5). The reticulocyte counts remained stable.

DISCUSSION

In this study, the absolute index proved satisfactory for marrow quantitation, although more precise methods are available. 6,19,24 The rate of reduction in cellularity of therapeutically irradiated human marrow in this study is similar to that reported by Choné. 8

Direct cellular destruction and mitotic inhibition are apparently responsible for the observed cellularity changes in marrow. The early granulocytes and particularly the

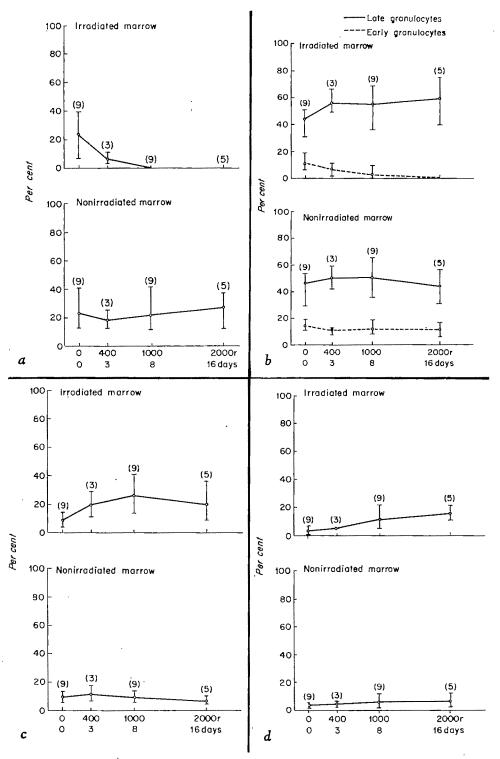


Fig. 3. Comparisons of relative percentages of nucleated cells in irradiated and nonirradiated marrow (number of patients studied in brackets). (a) Percentage normoblasts. (b) Percentage granulocytic forms. (c) Percentage lymphocytes. (d) Percentage monocytes.

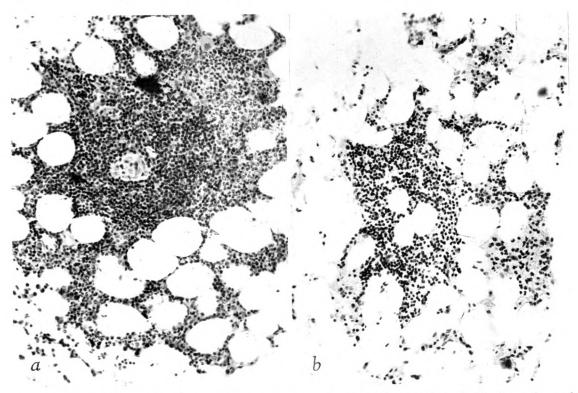


Fig. 4. (a) Lymphoid follicle with germinal center in a normal marrow tissue section. (b) Persistent focus of lymphocytes after 2,300 r in 17 days (hematoxylin and eosin; ×200).

early normoblasts are very radiosensitive; the initial fall in irradiated marrow cellularity was due to disappearance of these rapidly dividing cells. The slightly increased

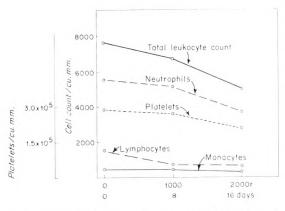


Fig. 5. Observed changes in mean platelet and total leukocyte counts during radiation therapy of 6 patients. The absolute differential for neutrophils, lymphocytes, and monocytes is the product of the relative differential for each cell line and the total leukocyte count.

disappearance rate for normoblasts in comparison with early granulocytes may reflect the shorter marrow turnover time for the erythroid precursors rather than increased radiosensitivity. Nuclear fragmentation in normoblasts may be either the consequence of radiation karyorrhexis or abnormal mitotic division. The observed internuclear bridging between normoblasts and the appearance of granulocytic giant cells are described by Fliedner and his associates^{7,8,23} as "mitotically connected" abnormalities.

Although the mitotic indices of irradiated marrow were not quantitated, it was apparent that mitotic activity was reduced by the third day of therapy and absent on subsequent aspiration smears. This observation has been noted by others. The relative persistence of polychromatophilic and orthochromatic normoblasts and late granulocytes reflects the halt in mitoses of the earlier stages with continuing maturation of these elements.

The relative increase of locally irradiated marrow lymphocytes has been reported by others,5,9,11,20 although this study demonstrated a moderate reduction in the lymphocytic absolute index by the sixteenth day of therapy. The persistence of lymphocytes is difficult to explain. Lymphatic tissue has been considered the most radiosensitive tissue, since the original observation by Heineke. Perhaps the lymphatic foci, which proved to be persistent, serve to replenish locally depleted marrow lymphocytes. Lymphatic foci in other body organs have been reported as radioresistant, such as in the intestinal mucosa where lymphocytes may be 15 times more radioresistant than those in peripheral lymph nodes.²² If, instead, the persistent lymphocytes are derived from the peripheral circulation, their relative radioresistance could be explained by the work of Trowell who found that circulating lymphocytes were 6 times more radioresistant than were lymph node lymphocytes. The effects of "irradiation shock" with deposition of circulating lymphocytes into irradiated marrow, as well as into other tissues, producing a secondary lymphopenia is another suggested explanation.11

The persistence of monocytes is suggestive of a radioresistance of mature monocytic forms. Nuclear and cytoplasmic vacuolation in the monocytes of irradiated marrow may represent stress changes or stages in transition of becoming macrophages.

Although megakaryocytes did not appear affected after 400 r in 3 days, only a rare megakaryocyte survived 8 days of therapy and some of these demonstrated karyolysis. Since their estimated lifespan is 25 days,⁴ megakaryocytes probably are directly destroyed by irradiation.

The histologic sections of the irradiated marrow demonstrated an apparent increase in number of plasma cells; yet, the differential marrow counts did not reflect a relative increase in plasma cells in this study. A sampling error may have been introduced since nucleated cells in the feather edge of marrow smears were not counted. Also, the

perivascular location of plasma cells may impair their aspiration with "marrow juice" in representative quantities.

There was no radiation effect on the marrow outside the fields of irradiation (abscopal effect).16 This observation is consistent with the recent report by Goswitz and associates. If an abscopal effect is denied, the origin of the mild reduction in leukocyte and platelet counts during focal irradiation is difficult to explain. A search for a circulating leukotoxin by others has been unrewarding.^{2,18,17} The absence of peripheral blood cell degeneration in this and other studies9,21 makes a direct effect on circulating elements in the beam of radiation unlikely. Lawrence and associates12 suggested that a scatter effect of radiation exposing a greater volume of marrow than generally considered may produce leukopenia, while Goswitz and co-workers considered possible sequestration of leukocytes by radiation-altered tissues.

SUMMARY

The acute effect on hematopoiesis of focal irradiation to bone marrow was evaluated by serial morphologic studies of aspirates from irradiated and from distant marrow sites during radiotherapy of 9 patients with cancer.

In the irradiated marrow, the erythroid line showed marked reduction of early precursors at 400 r and complete disappearance of all nucleated cells at 1,000 r. The granulocytic line did not demonstrate marked reduction of early forms until 1,000 r had been delivered; giant granulocytes were most prominent at 1,000 r. Marrow lymphocytes were surprisingly persistent in the irradiated marrow; preservation of lymphocytic foci was noted in histologic sections of marrow at 2,000 r. Monocytes demonstrated cytoplasmic vacuolation at 400 r and tended to persist even at 2,000 r. Megakaryocytes were rarely noted after 1,000 r marrow irradiation. Histologic sections of marrow particles confirmed the hypocellularity of irradiated marrow. Plasma cells and reticular cells proved to be resistant to these doses and were conspicuous in the histologic sections.

Consistent changes were not noted in the nonirradiated marrow samples. A mild depression of circulating blood neutrophils, lymphocytes, and platelets occurred without evidence of degenerative changes in these elements. The absence of a radiation effect on the nonirradiated marrow may have been due to the relatively small volume of marrow irradiated in the treatment fields.

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CYLINDROMA*

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CYLINDROMA is a time honored word for a type of adenocarcinoma arising in salivary gland tissue. Although the word was first coined by Billroth² in 1859 to describe the gross structural pattern of the stroma of these tumors, the term usually brings to mind the characteristic microscopic pattern. The clinical picture in this, as in other types of salivary gland tumor, has been concisely described by Foote and Frazell4 in their monograph and more recently by Moran et al.7 The radiologic literature concerning this type of salivary gland tumor varies from describing them as "radiosensitive . . . and probably radiocurable"8 to statements that radiation response is "generally unsatisfactory."4

From a recent review of a small number of these tumors treated at the Norwegian Radium Hospital over a 25 year period, it appears that some of this confusion regarding the radiosensitivity and radiocurability of this tumor may arise from an error in histologic diagnosis.

MATERIAL

We have recently reviewed the case histories of 445 tumors of the major salivary glands treated at the Norwegian Radium Hospital prior to 1958. We have not separated parotid from submaxillary and sublingual gland tumors. Among these were 34 cases that were originally diagnosed as cylindroma, or one of its synonyms. The histologic sections were still available for review in only 30 of these cases and of these 18 proved to be some other type of salivary gland tumor. As Foote and Frazell⁴ have pointed out, it was formerly common to include this diagnosis with some cellular benign mixed tumors which showed a

superficial resemblance to this histologic pattern in some areas. Seven cases in this material were of this type and need not be discussed further. Two others were adenocarcinomas of salivary gland which showed a quite different histologic pattern from cylindroma. The other 9, however, showed a pattern of "adenoid cystic" type which could be quite confusing histologically, and these will be described more fully.

PSEUDOCYLINDROMA

We have classified a uniform histologic pattern of "adenoid cystic" type in tumors showing some myxoid or pseudocartilaginous stroma as mixed tumor variants. The general pattern of these tumors, particularly under low power magnification, could easily lead to an erroneous diagnosis of cylindroma. The 9 cases assigned to this group are an incidence half as great as of cylindroma in this series. Since the histology of all cellular mixed tumor cases which received postoperative irradiation at this hospital was not reviewed, the incidence may be even larger.

One tumor in this group was histologically malignant (Fig. 1). This was in a 64 year old woman (#1446/44) who was seen after the second excision of a parotid mass and was given "prophylactic" irradiation. The mass had been present for about 20 years before the first excision. With a radium teletherapy unit, 4,100 r (skin) was delivered in 8 days. In spite of this, the tumor recurred locally and in regional lymph nodes in 6 months and showed no response to an additional 3,550 r (skin) in 15 days. She died 2 years after the first radiation treatment.

Three other tumors were histologically

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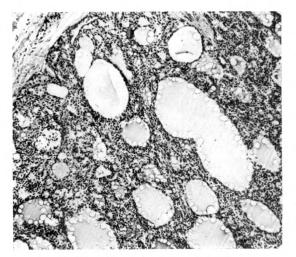


Fig. 1. Adenoid cystic pattern in malignant mixed tumor.

benign, but the patients ultimately died of cancer. One was treated after biopsy only. This was Case #199/35, a 59 year old woman with a tumor in the parotid 7 cm. in diameter and adherent to the skin, which had progressed slowly over 4 years. A salivary fistula was present. After biopsy (Fig. 2) radium teletherapy was given to 4,500 r (skin) in 10 days. The mass regressed to 3 cm. in diameter 9 months later and the fistula closed. An additional 3,150 r in 9 days gave no further regression. Within 2 years the mass progressed and ulcerated in spite of electrocoagulation and interstitial

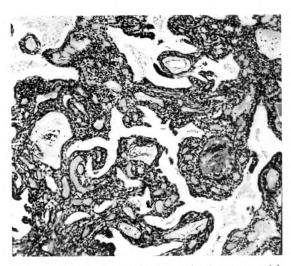


Fig. 2. Histologically benign mixed tumor with adenoid cystic pattern.

radium treatment, and the patient died with massive local disease 6 years after the first treatment.

The second case (#1487/46) was a 68 year old man with a submandibular mass for only 1 year. This was excised and at the time of irradiation, 3 months later, there was only vague induration beneath the scar. Radium therapy to 4,100 r (skin) in 8 days was given and produced no softening; an additional 3,600 r in 7 days was added 4 months later. In spite of this, the tumor recurred by 1 year, ulcerated, and the patient died less than 4 years after initial treatment.

The third patient was seen following inadequate excision and was re-operated on at this hospital, followed by minimal irradiation (#678/52). He succumbed to lung and bone metastases in less than 3 years.

The other five tumors—Cases #1992/46 (Fig. 3), #485/49 (Fig. 4), #2038/50, #1978/52 and #1954/53 (Fig. 5)—were benign histologically and clinically. The patients following extirpation of the tumor were without palpable recurrence. They were irradiated with 4,000–5,000 r skin dose with a radium bomb in 8 to 15 days, and all are well for a period of more than 10 years, 1 for more than 15 years.

The clinical picture of malignancy arising

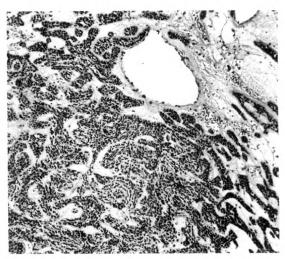


Fig. 3. Cellular mixed tumor simulating a cylindroma. Histologically and clinically benign.

in histologically benign mixed tumors is an unusual occurrence. About 2 per cent of patients with other benign mixed tumors in this series ultimately died of malignant mixed tumor. The malignant course in 4 of these 9 cases with the adenoid cystic pattern in mixed tumors would suggest that the prognosis is ominous for patients with this type of salivary gland tumor. This is contrary to Foote and Frazell's4 findings that these were always benign (see Fig. 21 of this reference, identical to Case #1487/46 above). In this small series, however, the prognosis was better than for patients with true cylindroma. The response to irradiation for this tumor is difficult to judge, but probably is as poor as in other forms of mixed tumors of the salivary gland.

CYLINDROMA

Among the remaining 18 cases with presumed cylindroma, 2 received surgical treatment only. Sections were not reviewed in these cases, although one remains well over 5 years.

Sixteen cases received irradiation as part of their treatment, and sections were available for review in 12 of these, as enumerated below.

The microscopic examination in these tumors showed small darkly staining cells

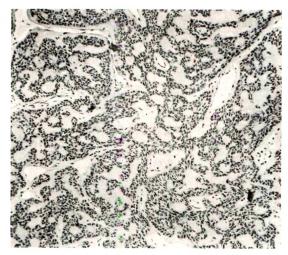


Fig. 5. Anastomosing cords of epithelial cells in myxoid stroma. Benign mixed tumor variant.

with less obvious cytoplasm than some of the pseudocylindromas, less variation in cell size, and an absence of myxomatous or pseudocartilaginous stroma. Typical patterns are shown in Figures 6 and 7. Nine of these cases were seen following a surgical procedure, often merely local excision. Two were reoperated on by radical parotidectomy prior to irradiation. Only one of these had developed local recurrence, but both died of lung metastases at $2\frac{1}{2}$ and $3\frac{1}{2}$ years following their hospital admission. Seven other cases were seen postoperatively with-

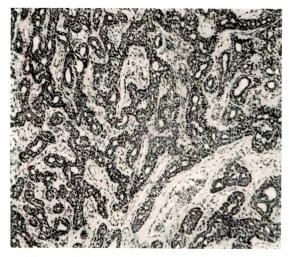


Fig. 4. Benign mixed tumor with adenoid cystic pattern.

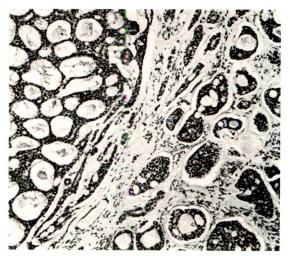


Fig. 6. Typical cylindroma showing variable amount of stroma and acellular areas.

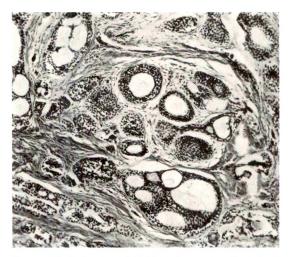


Fig. 7. Cylindroma with fibrous stroma. Recurrent tumor which showed good response to irradiation.

out palpable recurrence and were irradiated with a 3 gm. radium bomb at 6 cm. source skin distance. The usual dose was about 4,000 r to the skin in 8 to 9 days to a 6 or 8 cm. diameter field. This delivered approximately $\frac{2}{3}$ of this dose at 2 cm. and $\frac{1}{3}$ at 5 cm. depth. One of these patients (#1226/47) died of heart disease I year after irradiation. The histologic section was not available in this one of the q cases. Two of the others died of metastases, 17 and 24 months after treatment without local recurrence (#1056/45 and #206/47). Two patients survived without evidence of recurrence until death from cerebral vascular disease, 13 and 16 years following treatment (#1403/43 and #157/40), and I is still well at 14 years (#3985/49, Fig. 6). It is doubtful that irradiation had any part in salvaging these 3 cases. The only difference in the history from that of the 2 patients dying of metastases was that they had had multiple previous surgical procedures, while the survivors had no previous inadequate excisions. One patient (#1945/56) was apparently well for 7 years until a recurrent nodule in the scar was removed recently and again showed cylindroma.

In attempting to assess the radiosensitivity of this type of tumor, we found only 6 patients who were treated for a palpable recurrence, all of whom died of cancer, and

only I who was treated primarily with irradiation. Unfortunately, in 2 of the former and the solitary latter case, the sections are no longer available for review. Two of the 4 cases confirmed histologically showed a good radiation response in the recurrent tumor. This is comparable with the report of Ahlbom¹ that 8 of 21 cases showed a marked immediate response to radiation (in minimal dose) similar to that seen in lymphoma.

One case showing a marked radiation response in this material (#67/33, Fig. 7) presented with a recurrent mass, $8 \times 8 \times 3$ cm., beneath the scar from surgery, which had been performed 18 months previously. The patient was treated with the radium bomb to an 8 × 8 cm. field, receiving 2,400 r to the skin in 5 days, and following a 60 day rest, an additional 3,300 r in 7 days, or a total of 5,700 r to the skin. By the beginning of the second series of treatments, the mass had regressed to $7 \times 5 \times 2$ cm. and 4 months later to only a vague deep induration. Less than 2 years later, the mass again recurred to a size of 6 cm. in diameter. There was no response to a dose of 1,000 r to the skin which was repeated 3 times at 3 month intervals, and the patient died with extensive local disease 7 years after the first treatment.

One other case responded only to massive surface doses of radiation. This was a 49 year old man (#279/46) with a recurrent mass, 4 cm. in diameter. This regressed to approximately 1.5 cm. in diameter 5 months after a dose of 4,600 r to the skin was delivered in 9 days with a radium bomb. Admittedly, this was only about 1,800 r in the deepest part of the tumor. A recurrent mass was noted by the eleventh month, at which time 25 mg. of radium needles were inserted into the mass for 1,200 mg. hours. The tumor again regressed but recurred prior to the third year, causing death $4\frac{1}{2}$ years after the first treatment.

One other case, in which the histology could not be reviewed, was treated in the very early days of the hospital with a radon bulb (#147/38). A dose, estimated at about

13,000 r, surface, caused some regression of a recurrent mass which ultimately progressed and caused death 7 years later. Three cases, of which 2 had the histology confirmed, showed no significant response to rather intensive irradiation. Two (#667/ 44 and #438/42) were treated with the radium bomb to 4,100 r in 8 days, and 4,600 r in 9 days to the skin overlying a recurrent mass with satellite skin nodules. The third case $(\frac{\#3}{42})$ had 4,100 r delivered to the skin in 17 days to a 100 cm. square field with 175 kv. roentgen rays at 50 cm. target skin distance. None of these cases showed a measurable decrease in the size of the recurrent mass.

The only case treated primarily with irradiation had no section available for review (#378/38). A mass about 3 cm. in diameter was treated to 4,600 r (skin) in 14 days with a radium bomb. There was regression for a few months, but by the fifth month the tumor measured nearly 4 cm. in diameter. This was then excised and reported as a cylindroma; additional irradiation of 2,600 r to the skin was given in 4 days. The patient died of hypertension 12 years later without recurrence.

In résumé, the estimate of radiation sensitivity of cylindroma of the major salivary glands, from this brief series, is that only transient regression of known recurrent disease was produced with quite aggressive irradiation.

We have not attempted to review all salivary gland tumors in aberrant locations treated at this hospital. A series of such cases in the oral cavity and pharvnx was reported by Hobaek⁵ some years ago. Unfortunately, the sections on these cases are no longer available for review, but 19 aberrant salivary gland tumors were reportedly cylindromas. A correlation of regression with dose could be made in only 6 of these. Three received under 4,000 r tumor dose in 10 to 21 days and showed regressions lasting less than 2 years. Three others received over 6,000 r tumor dose in similar time periods and the tumors regressed for an average time of approximately 4 years.

We found only 2 cases of cylindroma of the trachea treated at this hospital, one of which was previously reported by Engelstad³ in 1937. This patient was treated with 175 kv. roentgen therapy through 4 oblique fields, receiving a total of over 14,000 r to the skin. Although there was symptomatic improvement following this treatment, there was recurrence at 2 years which did not respond to re-treatment and caused death 5 years after the first treatment.

We found only 1 other case of cylindroma of the trachea treated since this time. This patient (#2854/60) was treated by a 31 mev. betatron, receiving 4,150 r (as measured by a Victoreen r meter) tumor dose in 48 days followed some months later by an additional 2,000 r in 13 days. This produced a similar response to the one in the previous case with recurrence at $2\frac{1}{3}$ years. There was slight response to an additional 4,600 r and this patient is still living with local disease and bone metastases, more than 4 years after the first treatment. This is in agreement with 3 cases of this tumor in the bronchus reported by Markel et al.,6 only 1 of which survived over 2 years after irradiation.

Although the number of cases in these aberrant areas is also small, it does not appear that cylindroma in these sites is any more sensitive than in the major salivary glands.

SUGGESTED MANAGEMENT OF CYLINDROMA

The infiltrative nature of growth, including perineural infiltration, has been reported in previous descriptions of this tumor. 4.7 Wide surgical removal may thus be easier to recommend than perform. Nearly half of the cases in this series had local recurrence following resection. Since one local recurrence was noted after 7 years, it is possible that many of the others who succumbed to distant metastases, did not have time for local recurrence to become clinically evident. Although only 1 of 7 cases given "prophylactic" postoperative irradiation showed local recurrence, the

minimal response of known recurrent parotid cylindroma, and of this tumor in other sites, would cast doubt on the benefit of such irradiation. Particularly in larger tumors, it would seem more logical to utilize the slight radiation response to reduce the peripheral infiltration of the tumor to the limits of a radical removal of the involved gland. For this preoperative irradiation, or when irradiation is given for palliation in nonresectable areas, the radiation dose should be carried to the maximum tolerated by surrounding structures. Because of proximity to bone and the need for subsequent surgical intervention, supervoltage irradiation seems mandatory. If the tumor is accessible, but not resectable, a supplemental necrotizing dose of interstitial radiation with radium or other source should be considered.

SUMMARY

A diagnosis of cylindroma should conform to rigid histologic criteria. A similar epithelial pattern in a myxoid or chondroid stroma is presumably a variant of mixed tumors of the salivary gland. Many of these tumors will have a clinically malignant course.

True cylindromas show temporary response to intensive irradiation. Although the only curative treatment appears to be

surgical, preoperative irradiation may be beneficial in decreasing the incidence of local postoperative recurrence. Irradiation, whether preoperative or palliative, should be carried to the maximal dose tolerated by surrounding normal structures.

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LYMPHANGIOGRAPHY AS AN ADJUNCT TO PELVIC RADIUM DOSIMETRY*

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THE present work deals with calculation of dose to the ilio-pelvic lymph nodes in the radium treatment of carcinoma of the uterine cervix, utilizing lymphography to identify the location of the lymph nodes.

The radiotherapeutic attack on this disease is traditionally twofold, and generally parallels the two major elements of the disease. The local primary tumor is most effectively treated by intracavitary radium, which, because of its physical characteristics, permits an extremely high dose to the primary tumor while keeping the dose to neighboring normal tissues within a tolerable range. Lateral parametrial extension and first echelon lymph node metastases are best treated with supplemental external irradiation with which one can bring a large block of tissue to a rather homogeneous, controlled dose.

The curability of the primary lesion and lymph node metastases depends among other factors on the adequacy of the radiation dose. In order to cure a maximum number of patients, the radiation tolerance of normal pelvic organs must be reached if not exceeded in some individuals. It is, therefore, essential that the contribution of both radium and external radiation be accurately known so that, if necessary, maximum doses of each can be given, but normal tissue tolerance not be exceeded.

It is for this reason that the dose from radium to the ilio-pelvic lymph nodes is important. This dosage contribution from radium alone is inadequate to be relied upon, but it must be accurately known in order to decide the dose of external radiation needed. By performing lymphography



Fig. 1. Anteroposterior roentgenogram of intracavitary radium applicator and opacified iliopelvic lymph nodes.

prior to radium insertion, one obtains roentgenograms on which both the radium sources and the lymph nodes are easily identifiable (Fig. 1 and 2). By using the principle of orthogonal projection, the distance(s) from each radium source to any given lymph node(s) can be easily determined. Knowing the distance from each source to a given lymph node and the strength of the source, the dose from each source is obtained by the inverse square law, and the dose from the entire implant is merely the sum of the individual doses from each source.

One of the earlier and important works

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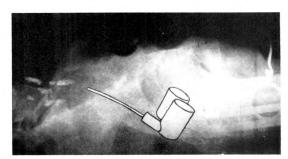


Fig. 2. Lateral view of Figure 1.

touching on the subject of lymph node dosage from radium was that of Tod and Meredith, who described points A and B. Point A was defined as located 2 cm. up from the lateral fornix and 2 cm. lateral to the cervical canal. Point B was taken as being 3 cm. further lateral to point A. The dose to point A was represented as indicating the tumor dose, while the dose to point B was regarded as approximating the dose to the pelvic wall or "lymph node bearing areas." 8.15

Kottmeier,¹³ Fletcher *et al.*⁴ and Gorton⁷ each realized the need for more specific information about lymph node dosage from radium and carried out actual measurements at the operating table by placing a dosimeter against the lymph node areas while the patient was undergoing lymphadenectomy with the radium still in place. Since their readings were in total dose rates from the entire radium system, it was necessary for them to actually change the loadings and then repeat the readings to learn the effects of different loading patterns.

The application of lymphography to this problem, enabling accurate measurements of radium-to-lymph-node distance to be made from the roentgenograms, seemed to offer several advantages. The relevance of this method as applied to carcinoma of the cervix depends on several factors: (1) the usual pattern of lymph node metastases in this disease, (2) the ability of lymphography to opacify all significant lymph nodes in the area, (3) the accuracy of determining the distance between two points

in space by means of measurements made from the anteroposterior and lateral roentgenograms, and (4) the applicability of the inverse square law to radium dosage for these distances.

(1) The usual pattern of lymph node metastases. Since one is not generally able to ascertain preoperatively whether a given patient has metastases to lymph nodes,3,19 and if so, which ones are involved, the approach to the individual patient must be guided by the probability of involvement of lymph nodes by metastases and by their probable locations. The anatomy of the lymphatic system in this region follows a basically simple organization.11,17 The lymph nodes are aggregated in clusters about the major blood vessels and bear the name of these vessels. There are the external iliac, common iliac, hypogastric, and juxta-aortic groups. The external and common iliac groups are further subdivided into three chains: the external chain being lateral to the artery, the middle chain in the sulcus between artery and vein, and the internal chain located medial to the iliac vein and somewhat prolapsed into the pelvis. The largest lymph node of this last chain, the middle

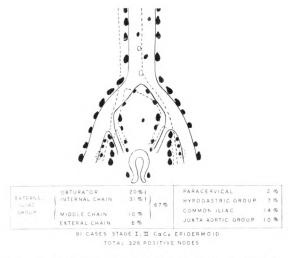


Fig. 3. Distribution of lymph node metastases in carcinoma of the cervix. (Reproduced with permission of J. Obst. & Gynaec. Brit. Emp.³)

lymph node, is quite constant and corresponds to the position of the so-called obturator lymph node.¹¹

Patients with Stage I disease have an average incidence of lymph node metastases of 16 per cent. This rises to 31 per cent in Stage II, and is higher for the later stages.8 In a study of the distribution of involved lymph nodes in 91 patients with Stage I and Stage II carcinoma of the cervix by Cherry et al.,3 76 per cent of the patients had involvement of the external iliac lymph node group alone. Only 5 per cent had involvement of the hypogastric group alone, while II per cent had metastases to both groups, but no others. Their results are tabulated differently in Figure 3, showing the percentage distribution of all positive lymph nodes. As has been found by others, 10 the external and common iliac chains were by far the most frequently involved, and most patients demonstrated an orderly sequence of metastases. 2,3,10,12,18 The external (or hypogastric) group was usually the first involved, followed by the common iliac and



Fig. 4. Frontal view of a bony pelvis containing wire of known length.

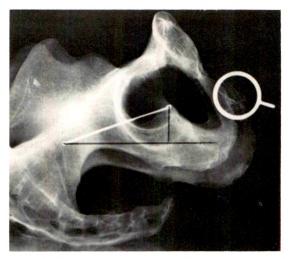


Fig. 5. Lateral view of Figure 4.

then the juxta-aortic groups, with only 8 per cent of patients showing exception to this sequence.³ Within a given group of lymph nodes, however, the involvement was not necessarily orderly; a more distant member of the group might be involved before a closer one. Members of the external iliac group were found to be positive, while the "obturator" lymph node, the closest member, was uninvolved.³ The implication of this finding is that one probably ought not to ascribe particular significance to any one lymph node, but ought rather to think in terms of lymph node groups.

- (2) It is our belief that lymphography usually opacifies all the aforementioned lymph node groups, contrary to the opinion of several other workers. 6,9,16 This is confirmed by the observation that of more than 25 patients coming to lymphadenectomy at our hospital following bilateral lymphography, not a single removed lymph node was found to be free of contrast material.
- (3) The accuracy of the orthogonal projection scheme was tested by making the standard exposures of a bony pelvis in which had been placed an opaque wire of known length (Fig. 4 and 5). Its length was calculated from the standard roent-genograms and the calculated length

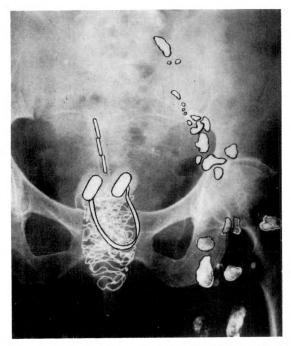
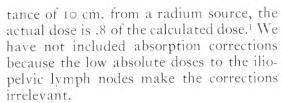


Fig. 6. Anteroposterior roentgenogram with opacified lymph nodes and intracavitary radium application. Compare to tracing in Figure 14.

agreed quite well with the actual length.
(4) Applicability of the inverse square law to radium dose calculation. For distances less than 5 cm. from radium sources, the actual dose is very close to that calculated by the inverse square law, because scatter balances absorption. At greater distances, absorption effects predominate: at a dis-



TECHNIQUE

The method of lymphography is described elsewhere. Briefly, it consists of cannulating a small lymphatic on the dorsum of the foot and then injecting an oily contrast agent over a 1 hour period. Subsequently, the intracavitary radium insertion is carried out in the usual manner, following which anteroposterior and lateral roentgenograms of the pelvis are taken. A metallic ring of known diameter is placed at the midplane in order to permit assessment of the degree of magnification resulting from the divergent rays (Fig. 6 and 7).

CALCULATIONS

In review, the orthogonal projection system is a method of determining the true distance between two points in space by projecting these two points onto two planes which are at right angles to one another (Fig. 8); for instance, the anteroposterior and lateral roentgenograms.

To determine the distance between one lymph node (N), and one radium source

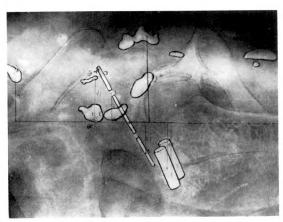


Fig. 7. Lateral roentgenogram. The uterine sources and colpostat as well as the lymph nodes have been retouched.

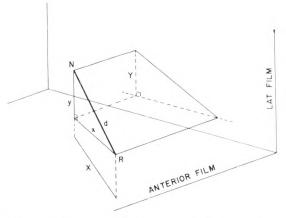


Fig. 8. Orthogonal projection system. N represents a lymph node, R a radium source. See text for explanation.

(R), a right triangle is constructed with the line joining the center of the lymph node to the center of the radium source forming the hypotenuse. The base becomes the length of image of line N-R as projected on the anteroposterior roentgenogram, and is taken directly off that film after correction for magnification (Fig. 9 and 10). The altitude of the triangle is obtained from the lateral roentgenogram by dropping a perpendicular from one of the points to a line which passes through the other point and is parallel to the film edge (Fig. 11 and 12). The length of this perpendicular is also corrected for magnification and then indicates the true height of the hypothetical triangle. The true distance between the two points is the square root of the sum of the squares of the other two sides. Then, applying the inverse square law, according to which the intensity of radiation from a point source varies inversely with the square of the distance from the source, and the relationship that I mc of radium delivers 8.25 r/hr. at 1 cm. distance, the dose rate from each source to each lymph node can be determined (Fig. 13). The dose to the node(s) from the entire system is the sum of the doses from the individual component radium sources.

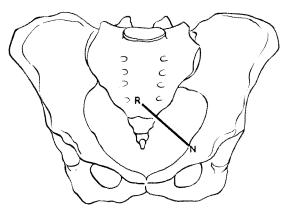


Fig. 10. Frontal diagram showing projection of N-R.

A small series of patients was studied by this method with dosages being calculated to representative lymph nodes in each of the major groups (external and internal chains of the external iliac group, the common iliac group, and the hypogastric group), as well as to Points A and B.

RESULTS

As was expected, 4,7,13 the dose to the lymph nodes bore no constant relationship to the dose delivered to Point B, but was considerably lower. The reasons for this are obvious from a consideration of the anatomy. Lymph nodes that appear on

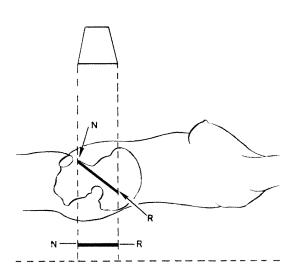


Fig. 9. Frontal diagram showing projection of distance N-R onto anteroposterior roentgenogram.

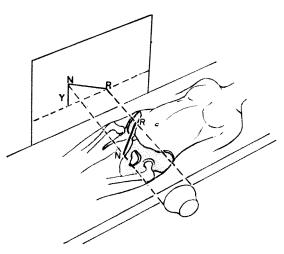


Fig. 11. Lateral diagram showing projection of distance N-R onto lateral roentgenogram and construction of triangle to obtain altitude Y.

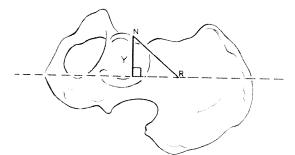


Fig. 12. Lateral diagram showing construction of altitude.

the anteroposterior roentgenogram to lie against the pelvic wall, virtually superimposed on Point B, are seen on the lateral roentgenograms to be situated far anteriorly (compare lymph node EI-E on anteroposterior and lateral tracings in Fig. 14 and 15). It is also apparent that the uppermost lymph nodes of the common iliac group are quite far removed from the radium system. Finally, Point B is defined with reference to the cervix, not to the bony pelvis, and therefore has a variable position with respect to the latter.14 The actual distance from the radium system to the lymph nodes is generally greater than that to Point B (Table 1).

The common iliac lymph nodes and the external chain lymph nodes of the external iliac group consistently received the lowest dose, the common iliacs ranging between 3-7 r/hr., and the external chain lymph nodes receiving between 4-11 r/hr. The dose rate to the common iliac lymph nodes was from $\frac{1}{3}$ to $\frac{1}{2}$ of the dose rate to Point B (and was usually less than 1/10 the dose to Point A). This means that if one planned

METHOD OF CALCULATION

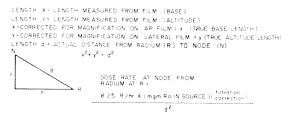


Fig. 13. Method of calculation.

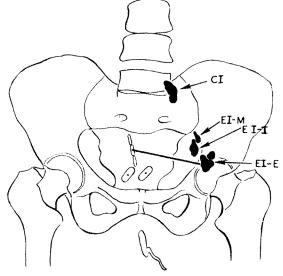


Fig. 14. Tracing of Figure 6. CI=common iliac group; EI-M=external iliac-middle chain; EI-I=external iliac-internal chain; EI-E=external iliac-external chain.

to deliver 7,000 r to Point A, some of the lymph nodes might receive less than 700 r from radium (Table 11).

The hypogastric group and the internal lymph nodes of the external iliac group usually received a dose comparable to Point B, but often received as little as $\frac{1}{2}$ that dose.

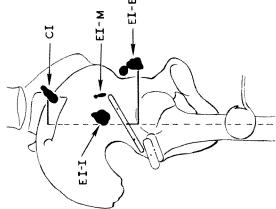


Fig. 15. Tracing of Figure 7. CI=common iliac group; EI-M=external iliac-middle chain; EI-I=external iliac-internal chain; EI-E=external iliac-external chain.

TABLE I
DISTANCE TO LYMPH NODE GROUPS

Group or Point of Interest		Distance (cm.) from Uterine Tandem 2 cm above Cervical Os		
Point		Mean	Range	
Point A		2		
Point B		5		
External Iliac Group	external chain middle chain internal chain	8.5 8.3 6.4	7.6-11.0 6.0- 9.1 6.0- 7.1	
Common Iliac Group		9.3	7.3-10.7	
Hypogastric Group		5.9	4.7- 6.9	

Our findings agreed with those who carried out direct measurements. The more anterior the radium, the higher was the dose to the lymph nodes. Therefore, the intrauterine tandem contributed more heavily than the vaginal radium, and a more anterior position of the entire implant would result in a higher dose to these lymph nodes.

SUMMARY

Lymphography provides a useful method of determining the radium dosage to any given lymph node or group of lymph nodes. It is convenient and does not depend upon measurements made at the operating table.

Also, since the contribution of each source in the system is determined individually, one is able to learn the effects of different source distribution by mathematical means rather than by manipulating radium sources.

Point B is seen to be a poor indicator of lymph node dosage. The average ratio of the dose to Point B to that of the middle lymph node of the internal chain of the external iliac group was .6; to the common iliac group, .3; and to the hypogastric group, the ratio was 1. The variable, but generally low, doses delivered to the lymph nodes are in accord with what anatomic considerations would imply and are in

TABLE II

Radium Dosage to Major Lymph Node Groups Compared with Point A and Point B	Dose Range r/hr.	Average	Average Ratio to Point B	Average Ratio to Point A
External Iliac Sexternal chain Group internal chain	4-11 6-13	7 10	~1/2 ~3/5	$\sim 1/8$ $2/11$
Common Iliac Group	3-7	5	~1/3	1/11
Hypogastric Group	10-18	15	~ 1	~1/4
Point B	14-19	1 7		, , , , , , , , , , , , , , , , , , ,
Point A	42-70	55		

agreement with the measurements made by others.

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THE PLACE OF LYMPHANGIOADENOGRAPHY IN THE DIAGNOSIS AND DURING THE TREAT-MENT OF MALIGNANT DISEASES*

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DEVELOPMENT of a simplified lymphangiographic technique^{2,13} and the accumulated experience in the interpretation of lymphangioadenograms^{7,11} are advances which permit adequate *in vivo* study of lymphatic pathology, useful for the orientation and evaluation of various forms of treatment. The injected contrast medium remains in the lymphatic system in decreasing concentration for several months, thus allowing for further observations, such as changes induced by the therapeutic methods employed.

In Table 1 the actual and potential uses of the method are listed.

The large number of lymphangioadenographies performed at our institution motivated retrospective analysis of the cases referred for treatment or consultation to the Division of Radiation Therapy, University of Miami School of Medicine, Miami, Florida. The study was undertaken to determine the degree of accuracy in the interpretation of lymphangioadenograms, the merits of this roentgenologic examination and the effects of radiation upon the lymph vessels and nodes.

MATERIAL AND METHODS

A total of 201 patients affected by histologically proven malignant diseases was selected from the first 700 successful lymphangioadenographic studies performed in the Department of Radiology. In most instances, the lymphographic study preceded the radiotherapy.

Twenty-seven patients affected by squa-

mous cell carcinoma of the uterine cervix underwent surgery. In these patients pathologic-roentgenologic correlation became possible. In 7 patients, lymphangioadenography was performed before and after radiotherapy was completed. Two cases were restudied several years after radiotherapy. A minor group of patients, comprising 13 with endometrial carcinoma, 6 with malignant testicular tumors, and 6 with squamous carcinoma of the vulva and vagina, were amenable also for radiographic-pathologic correlation.

Classification of these patients according to the histopathologic diagnosis is presented in Table II. For convenience, they have been arbitrarily divided into 3 groups, the most sizable one being represented by gynecologic neoplasms. The second group comprised patients with malignant lymphomas, and the third one was a miscellaneous group of patients with various malignant tumors which, with the exception of those affected by testicular neoplasms, are only summarily considered. Attention was particularly centered on the first 2 groups. An attempt was made to determine:

- (a) To what degree the lymphangioadenographic report correlated with the histology, when such was available.
- (b) How often the clinical staging of some of these patients had been influenced by the procedure.
- (c) Whether, and in what group of tumors, this diagnostic procedure had influenced the planning and the conduction of radiation therapy.

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Table I INDICATIONS FOR LYMPHANGIOGRAPHY

- I. Lymph Vessel Pathology:
 - a) Edema
 - b) Tumor
- II. Malignant Lymphadenopathies:
 - a) Metastatic
 - 1. Carcinoma
 - 2. Sarcoma
 - b) Lymphoma

For:

- a) Diagnosis
- b) Staging
- c) Treatment
 - 1. Radiation therapy
 - 2. Isotope therapy
 - 3. Chemotherapy
- III. Chromolymphography: Aid to surgical lymphangioadenectomy
- IV. Chylothorax, Chylous Ascites, and Chylous Reflux
- V. Protein-Losing Enteropathy
- VI. Experimental Studies:
 - xperimentai Studies a) Anatomic
 - b) Physiologic
 - c) Diagnostic
 - d) Therapeutic
- (d) During the follow-up period, the effectiveness of irradiation to the affected lymph nodes.
- (e) The lymphangioadenographic alterations induced in the lymph nodes and vessels which had been encompassed in the field of irradiation.

GROUP I. LYMPHANGIOADENOGRAPHY IN PATIENTS WITH MALIGNANT TUMORS OF THE FEMALE GENITAL TRACT

A. CARCINOMA OF THE CERVIX

Table III shows the distribution of 96 patients with squamous cell carcinoma of the cervix in whom an attempt of correlating the lymphangioadenographic findings with the clinical stage of the disease was made. Fifteen patients could not be staged when seen initially because they had previous treatment. A case of carcinoma of the cervical stump is included.

Table IV is a summary of the radiotherapy program and the average dose range of radiation employed in treating squamous cell carcinoma of the uterine cervix, at our institution, according to stage.

Among the 81 cases which were amenable to clinical staging, 30 had roentgenologic findings consistent with metastatic lymph node involvement, while in 48 of them the bilateral lymphangioadenographic study was interpreted as normal, and 3 had had a technically unsatisfactory study. Among the 15 patients in whom clinical staging was not possible, the roentgenologic abnormalities, in part, might be attributed to previous surgery and/or persistent disease (5 cases). In 7 of these patients the lymphangiographic findings were considered normal.

Since 27 patients underwent surgical procedures (26 had pelvic lymphadenectomy and 1 had exploratory laparotomy and biopsy of the para-aortic lymph nodes only), correlation of the lymphangiographic findings with histology of the lymph nodes was made (Table v).

In the 3 patients with Stage I disease, lymphadenectomy had not preceded the irradiation, and there was good radiographic-pathologic correlation.

Difficulties did arise in the Stage II group. Only 10 patients in this group underwent lymphadenectomy prior to irradiation; 5 patients received radiation therapy prior to lymphadenectomy; and I patient had an unsatisfactory study. Of the 4 patients in Stage II who had received preoperative irradiation, there was I false negative. Of the 3 patients with Stage III disease, 2 received preoperative irradiation. There was satisfactory correlation in this group since the case which was read positive lymphangioadenographically subsequently proved to have metastatic lymph nodes. The 2 patients with normal lymphangiograms who received preoperative irradiation had negative lymph nodes. Only I patient in Stage IV showed negative lymphangiographic findings, and subsequently no positive lymph nodes were encountered.

In the group of 14 cases staged prior to exploration and which received no radio-

Table II

201 patients with malignant neoplasms referred for radiation therapy at the university of miami, with lymphangioadenograms, according to histopathologic diagnosis

·				
I. Patients with Malignant	Squamous cell carcinoma of uterine cervix		96	
Tumors of the Female	Adenocarcinoma of corpus uteri		12	
Genital Tract:	Squamous cell carcinoma of vulva and vagina		6	
	Carcinoma of ovary		4	

				118
II. Malignant Lymphomas:	Hodgkin's disease		18	
11, 2,2,4,1B	Lymphosarcoma	8		
	Follicular lymphoma	4		
	Reticulum cell sarcoma	3		
	Mixed lymphomas	5		
	Mycosis fungoides	2		
	Unclassified	I		
			23	
			and	_
				41
III. Miscellaneous:	Tumors of the testis			
	(seminomas 6)		9	
	mixed tumors 3		-	
	Transitional cell carcinoma of urinary bladder		4	
	Squamous cell carcinoma of penis		3	
	Carcinoma of breast		5	
	Malignant melanoma		4	
	Other malignant tumors		17*	
	-		nonemag.	42
Total				201
Total				20

^{*} Includes metastatic tumors with questionable or unknown primary, soft tissue sarcoma, osteochondrosarcoma, etc.

therapy, 6 showed roentgenologic evidence of metastases and 7 had positive histologic studies. There was I false negative in which the positive lymph nodes were not in the location described lymphangiographically.

Table VI shows 7 patients with various stages of carcinoma of the cervix who had had pre- and post-irradiation lymphangio-adenography. Five of them underwent postirradiation lymphadenectomy. The studies were obtained from several weeks to several months following irradiation, and the purpose of presenting this group is to demonstrate the effects of irradiation on the pelvic lymph nodes and channels. Figure 1, A and B shows a patient, A.N., with a clinical Stage II-A carcinoma of the cervix. Note the uniformly decreased size of the lymph

nodes about 4 months following the initial study. In the 7 patients in whom no surgical procedure preceded irradiation, the second and sometimes third lymphangiographic study demonstrated clearly that, within the therapeutic range of irradiation, no alterations of the normal lymph flow pattern occurred. In contrast, the lymphangiograms of the patients who had had surgery prior to irradiation showed variable degrees of lymphatic abnormalities. Some of these may simulate persistent disease.

B. CARCINOMA OF THE UTERINE CORPUS

There were 12 patients with endometrial carcinoma; 6 of these with Stage 1 disease (Table VII). These patients received preoperative irradiation, and their lymph-

Table III

CARCINOMA OF THE UTERINE CERVIX: CORRELATION OF THE LYMPHANGIOGRAPHIC FINDINGS WITH THE CLINICAL STAGE OF THE DISEASE

	NI C	Lymp	hangiography	
Stage	No. of Patients	Indicative of Lymph Node Metastases	Normal Study	Technically Unsatisfactory
I-A I-B	7 3	I 2	6 1	
II-A II-B	25 8	6 3	17 4	2 I
III-A III-B IV	24 6 8	11 4 3	13 2 5	
No Staging: Stump Post surgery Post irradiation Recurrence	15	5	7	3*
Total	96	35	55	6

^{*} Previous surgery.

angiograms and histologic study showed no evidence of metastases. Two patients in whom the lymphangiograms indicated pelvic lymph node metastases underwent surgery, and a histopathologic confirmation was obtained.

In 2 cases which had carcinoma of the corpus with extension to the cervix (corporis et colli), lymphangiograms demonstrated diffuse lymph node involvement in 1 and no definite signs of metastases in the other. Radiotherapy consisted of cobalt 60

TABLE IV

RADIATION PROGRAM AND AVERAGE DOSE RANGE FOR SQUAMOUS
CELL CARCINOMA OF THE CERVIX, ACCORDING TO STAGE

Stage	External Irradiation*	Intracavitary Radium†
I. Early massive	minimum 2,∞∞ r total pelvis 3,∞∞ r-4,5∞ r total pelvis	5,∞-7,5∞ mg./hr. 4,5∞-8,5∞ mg./hr.
II. Early massive	3,∞0 r-4,500 r total pelvis	4,500–8,000 mg./hr.
	4,∞∞ r-4,5∞ r total pelvis	4,5∞-6,∞∞ mg./hr.
IIIIV. Stump	5,000 r total pelvis	4,∞∞-5,5∞ mg./hr.
	4,∞c r	Interstitial or cone intravagina applications

^{*} CO40 at FSD 80 cm.; parallel opposing ports ranging from 15 cm.×15 cm. to 10 cm.×12 cm.; average estimated weekly dose of 1,000 rads midplane.

[†] Usually in two applications of at least 2 weeks apart preceding or subsequent to external irradiation.

 $T_{\rm ABLE} \ V$ Histopathologic and roentgenologic correlation of Carcinoma of the uterine cervix: 27 patients

		Lymphangiograp			phy		Histopathology			
Ç.	No. of	N	Vo Irradiatio	on	Irrad	iation	Surger	y Alone		erative iation
Stage	Patients	Metas- tases	No Metas- tases	Technic- ally Unsatis- factory	Metas- tases	Normal	Lymph Nodes+	Lymph Nodes—	Lymph Nodes+	Lymph Nodes-
I	3	I	2				I			2
II	15	4	6	I	I	3	5	6*	2	2
III	3	I				2		I		2
IV	I		I							I
Hyster-										
ectomy	4	2	I			I	I	2		I
Stump	I		I							I
Γotal	27	8	11	I	I	6	7	9	2	9

^{*} One of these 6 patients had had technically unsatisfactory study.

irradiation and intracavitary radium. The patient in whom roentgenologic finding suggested diffuse metastases underwent surgery. Thorough lymphadenectomy and subsequent histologic study failed to demonstrate metastases. All of the extirpated lymph nodes, however, showed nonspecific lymphadenitis (Fig. 2).

C. SQUAMOUS CELL CARCINOMA OF THE ${\bf V}{\bf U}{\bf L}{\bf V}{\bf A} \ {\bf A}{\bf N}{\bf D} \ {\bf V}{\bf A}{\bf G}{\bf I}{\bf N}{\bf A}$

In this group, lymphangiography was performed prior to surgery, and there was satisfactory radiographic-pathologic correlation. In one of these cases the lymphangiographic study was indecisive for metastases because of some filling defects observed in the lymph nodes which were considered possibly due to the lymphadenitis. Subsequent surgery established that the filling defects were metastatic deposits. In 1 of the 6 patients, histopathologic correlation was not possible since surgery was not performed and the patient was treated by radiotherapy only.

GROUP II. MALIGNANT LYMPHOMAS

A group of 41 patients with histologically proven diagnosis of malignant lymphomas was studied. Table VIII shows the distribution of 23 patients with various forms of lymphomata other than Hodgkin's disease,

Table VI

SQUAMOUS CARCINOMA OF THE UTERINE CERVIX: CASES WITH LYMPHANGIOADENOGRAPHIES*

OBTAINED PRIOR AND SUBSEQUENT TO IRRADIATION†

Patient	Clinical	Lympha	Subsequent	
ratient	Stage	Pre Irradiation	Post Irradiation‡	Lymphadenectomy
L.P.	I-B	No lymph node involvement	Same; lymph nodes decreased in size	Not performed
P.P.	II-A	Suggestive for metastasis	Uncertain	Yes: all lymph nodes negative
A.N.	II-A	No lymph node involvement	Same; lymph nodes decreased in size	Yes: all lymph nodes negative
J.M.	II-A	No lymph node involvement	Same; lymph nodes decreased in size	Yes: all lymph nodes negative
M.M.	II-B	No lymph node involvement	Same; lymph nodes decreased in size	Yes: all lymph nodes negat/v
M.L.	II-B	Indicative of metastases	No metastases; lymph nodes smaller	Not performed
M.H.	III	No lymph node involvement	Normal; lymph nodes smaller	Yes: all lymph nodes negativ

^{*} Intervals between the studies from 6 weeks to several months after irradiation.

[†] All patients receiving combination of whole pelvis external irradiation and intracavitary radium.

[‡] Not a single post-irradiation study demonstrates alterations of the lymph channels or impairment of the lymph flow.

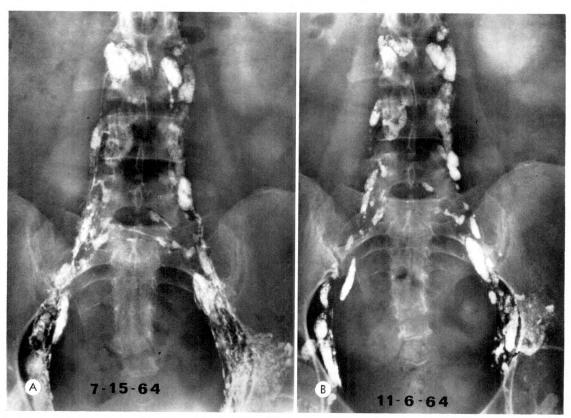


Fig. 1. (A and B) Frontal roentgenograms of the abdomen and pelvis before and after irradiation. Note slight reduction in the size of the lymph nodes.

in which predominance of lymphosarcomatous variety was evident (Fig. 3). There were 2 cases of mycosis fungoides included in this group.

Before lymphangiography, these patients

Table VII
ENDOMETRIAL ADENOCARCINOMA

		Lymphogra	ım	Histo-
	No. of Patients	Indicative of Lymph Node Nor Involvement		logic Metas- tases
I	6		6	0
II	2	I	I	I
Recurrence Corporis et		3	0	3
colli	2	1*	I	0
Total	13	5	8	4

^{*} False positive. Lymphadenectomy and careful histologic review of material showed only lymphadenitis.

with malignant lymphomas were classified into 2 groups: (a) localized and (b) generalized. For staging purposes, clinical findings and routine laboratory studies (blood cell count and chest roentgenogram) were considered. Table viii shows that after the lymphangiographic study, 5 of the 10 patients with apparently localized lymphomas demonstrated unsuspected lymph node involvement. In I of these patients, the lymphangiograms demonstrated abnormal lymph nodes not exhibiting the lymphoma pattern. This patient responded poorly to irradiation. The autopsy findings revealed generalized carcinomatosis and a primary pancreatic carcinoma. Among the 4 negative readings, I was of a patient with the clinical diagnosis of mycosis fungoides.

Table IX shows the distribution of 18 patients with Hodgkin's disease. The staging preceding lymphangiography was based on the Peters and Middlemiss⁶ criteria with

TABLE VIII
CLINICAL AND ROENTGENOLOGIC CORRELATION OF MALIGNANT LYMPHOMAS OTHER THAN HODGKIN'S DISEASE

Stage Prior to		Lymphangiography				
Lymph	nography generalized	Indicative of Lymph Node Involvement (generalized)	Negative for Lymph Node Involvement	Suggestive	Total	
10	13	17*	5†	Ι‡	18	

^{*} One patient with mycosis fungoides showed generalized lymph node involvement ("typical lymphoma").

† One out of 4 "negative" readings was a patient with mycosis fungoides.

the modifications detailed by Fayos *et al.*¹ Of interest is that 8 of 11 patients with Hodgkin's disease, Stages I-A, I-B and Stage II-A, had positive roentgenologic findings. The subsequent treatment was influenced by the procedure, and the patients were subjected to systematic irradiation of the involved lymph nodes.

In clinically advanced stages of Hodgkin's disease, lymphangioadenography invariably was abnormal. The therapeutic measures in advanced cases were influenced to a lesser degree by the lymphangiographic findings, since these patients would have received a combination of radiotherapy and/or chemotherapy according to their individual needs. In the great majority of patients with lymphangiographic findings characteristic of lymph node involvement by lymphoma, the typical, minute, rounded, scattered filling defects and/or coarse reticular pattern in the lymph nodes were encountered.

Figure 4 shows an abnormal Virchow-Troisier's left supraclavicular lymph node which prompted the biopsy. In this case, lymphangiography was useful as a guide for securing histopathologic material which proved the presence of unsuspected Hodgkin's disease. This patient exhibited no external manifestation of tumor amenable to clinical examination, and the presenting complaint was fever of unknown origin.

It is customary to obtain excretory urograms in the work-up of Hodgkin's disease. The excretory urograms may demonstrate obstruction and/or displacement of the ureters by the enlarged retroperitoneal lymph nodes. At times, however, the excre-



Fig. 2. Adenocarcinoma of the corpus uteri with extension into the cervix with chronic lymphadenitis. This case was misinterpreted as showing evidence of diffuse metastatic involvement. Histologic study of the involved lymph nodes showed no evidence of metastatic disease and the presence of chronic lymphadenitis.

[‡] A giant follicular lymphoma case which subsequently succumbed to generalized carcinomatosis from second primary malignant pancreatic carcinoma.

T	ABLE IX		
INFLUENCE OF LYMPHANGIOADENOGRAPHY IN	STAGING* AND	D TREATMENT	OF HODGKIN'S DISEASE

Stage		Stage Subs Lymphangio		Treatment		
Preceding the	No. of Patients			- Irradiatio	on Alone	Chemotherapy
Study	Tuttento	Unchanged	Changed to III	systematic	localized	and Local Irradiation
I-A	3	I	2	2	I	
I-B	3	I	2			3
II-A	5	I	4	4	I	
II-B	I		I			I
III-A	2	2		2		
III-B	4	4				4
Γotal	18	9	9	8	2	8

^{*} Staging follows closely the clinical criteria of Peters and Middlemiss, with modifications detailed by Fayos et al.1

tory urogram was normal in the presence of involved retroperitoneal lymph nodes (Fig. 5, A and B).

Lymphangiography is not only useful as a guide to the therapist for more rational planning of radiation therapy, but is also valuable as a means by which to observe



Fig. 3. Giant follicular lymphoma. Note marked enlargement of the lymph nodes which show rounded, disseminated filling defects and preserved margins.

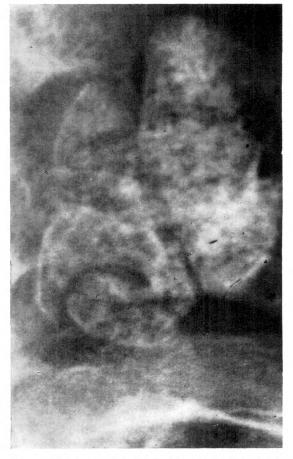


Fig. 4. Close-up view of left supraclavicular lymph nodes in a patient with Hodgkin's disease. Note coarse pattern in enlarged, rounded nodes (lymphoma pattern).

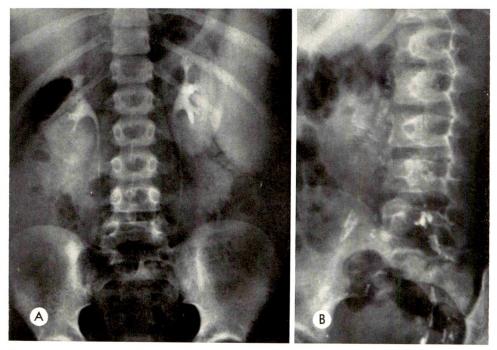


Fig. 5. Retroperitoneal lymphoma with normal intravenous urograms. (A) Normal intravenous urogram shows moderate splenomegaly. (B) Incompletely filled and large para-aortic lymph nodes are noted.

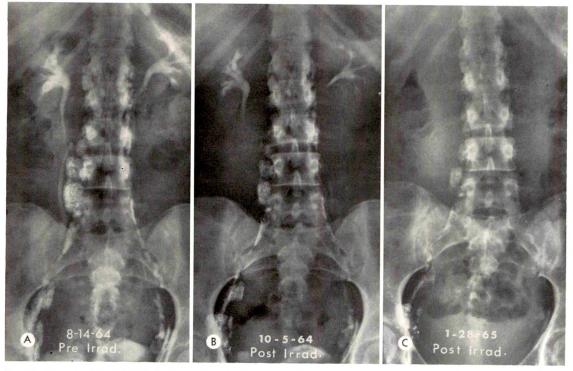


Fig. 6. Retroperitoneal lymphoma with slight ureteral deviation. (A) A concomitant intravenous urogram and a lymphogram show lateral deviation of the right ureter by adjacent enlarged retroperitoneal nodes. (B and C) Studies were obtained following irradiation. Both show marked decrease in the size of the involved lymph nodes.

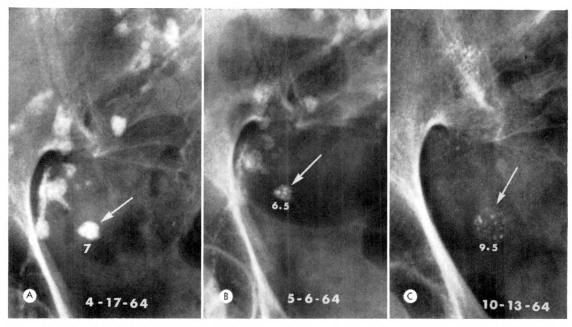


Fig. 7. (A, B and C) Hodgkin's disease; follow-up studies revealing recurrence of the disease. Note the progressive enlargement of a right pelvic lymph node. These observations covered a 6 month period, and enlargement of this lymph node was the only suggestion of recurrence of the disease.

the response to the irradiation (Fig. 6, A, B and C).

When the dose administered is low, or the treatment ports have not included all of the diseased lymph nodes, the follow-up lymphangiographic study may demonstrate the persistence and/or recurrence of the disease, hence amenable to additional irradiation.

Figure 7, A, B and C shows a patient with a clinically localized lymphosarcoma who received a dose of 1,600 rads midplane via cobalt 60 teletherapy in 2 weeks through a limited port.

On the contrary, when higher doses for treatment of lymphoma are used,⁶ prolonged arrest or sterilization of the disease is frequently achieved. This is usually manifested by marked reduction in the size of lymph nodes. However, roentgenologically, the abnormal architecture of lymphoma, in most instances, persists (Fig. 8, A and B; and 9, A and B).

During the follow-up period, the contrast material remaining in the lymph nodes may become insufficient for adequate determination of possible changes. Figure 10, A

and B shows a patient with Hodgkin's disease who showed diffuse lymph node involvement. Following a course of radiotherapy (estimated midplane dose of 3,000 r in 3 weeks using cobalt 60, focal skin distance 80 cm.), a roentgenogram obtained 8 months later showed reduction in the size of the lymph nodes which maintained normal architecture. Figure 11, A, B and Cshows the same patient following a second course of radiotherapy 3 years after the initial treatment. This treatment consisted of cobalt 60 teletherapy through a narrow port that encompassed the femoral, inguinal, and para-aortic regions to a dose estimated in the midplane of 3,000 rads in 3 weeks with the same factors. Reduction of lymph nodes ensued. Roentgenograms taken almost 2 years after the second injection (Fig. 12, A, B and C) still showed marked reduction in the size of the lymph nodes. Currently, this patient is seemingly free of the disease and enjoying excellent health.

GROUP III. MISCELLANEOUS TUMORS

In this group of miscellaneous tumors,

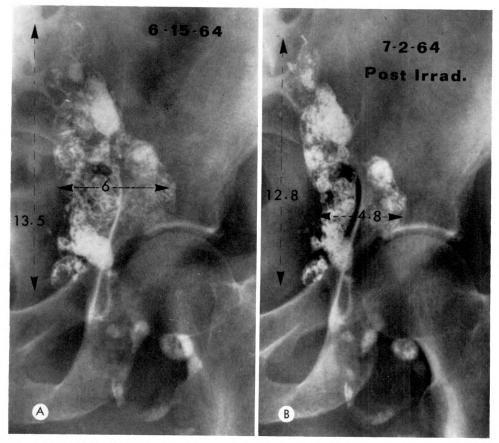


Fig. 8. (A and B) Retroperitoneal lymphoma showing marked reduction in the size of the lymph nodes following radiation therapy. Note that in only 17 days a marked reduction in the size of the lymph nodes has occurred. The lymph nodes maintain an abnormal architecture.

only malignant tumors of the testes are considered with some detail. Table x shows 9 cases of testicular tumors under study. There were 6 pure seminomas and 3 mixed tumors. Roentgenologically, lymph node involvement was reported in 6 cases of seminoma. Four patients with seminoma and 3 patients with mixed malignant tu-

mors of the testes had surgical exploration preceding radiation therapy. Correlation between clinical, roentgenologic, and histopathologic findings was attempted. In 2 patients with seminoma, this correlation was not possible because they underwent radiation therapy without exploratory laparotomy. The patients with seminoma

 $\label{eq:Table X} Table \ X$ malignant tumors of the testes

Diagnosis	No. of Patients with Lymphangiography	Abnormal Lymphogram Indicative of Lymph Node Metastases	No. of Cases with Subsequent Histo- logic Verification
Seminoma	6	3*	4†
Mixed tumors	3	3	3

^{*} All 3 had had histologically positive lymph nodes on exploration preceding the radiation therapy. \dagger Includes 1 patient with normal lymphangiogram and no positive lymph nodes encountered.

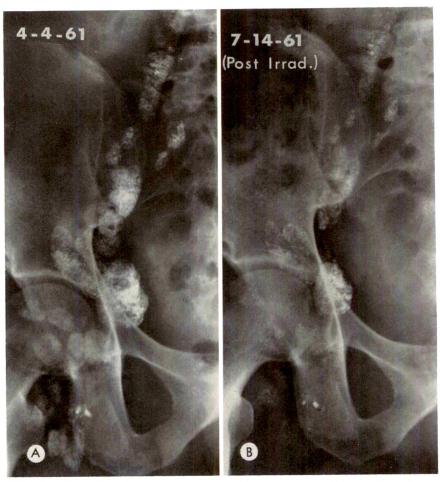


Fig. 9. (A and B) Retroperitoneal lymphoma showing radiation therapy effects. A was obtained 3 months after irradiation. Note moderate reduction in the size of the involved lymph nodes which maintain abnormal architecture.

exhibiting positive lymph nodes by lymphangiography were subsequently also subjected to thorough and systematic irradiation of the pelvic, para-aortic, and mediastinal lymph nodes; while the patients with mixed tumors underwent exploratory procedure with attempt of lymphadenectomy. The small number of cases does not afford the opportunity for statistical evaluation. This limited experience seems to suggest that lymphangiography is a useful procedure in the assessment of metastases and appropriate conduction of irradiation in patients affected by seminoma.

Follow-up lymphangiograms after irradiation were also obtained in some of the patients with seminoma. Figure 13, A, B

and C shows a patient who was explored after orchiectomy, and large retroperitoneal lymph node metastases were encountered. Lymphangiography subsequent to exploration revealed enlarged lymph nodes with filling defects and signs of lymph stasis. Lymphangiographic re-examination following radiotherapy showed a marked decrease in the size of the lymph nodes with remaining stasis.

Lymphangiography may also be used for evaluation of the thoroughness of adenectomy (Fig. 14, A and B).

The 3 cases with mixed tumors (teratocarcinomas with embryonal or other components) showed a different roentgenologic pattern from that of seminoma.

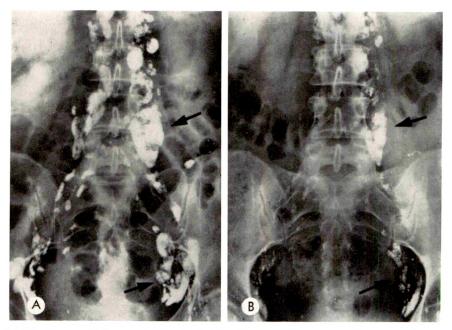


Fig. 10. Hodgkin's disease with retroperitoneal lymph node involvement. (A) Enlarged retroperitoneal lymph nodes with lymphoma pattern. (B) Reduction in the size of the lymph nodes following radiation therapy.

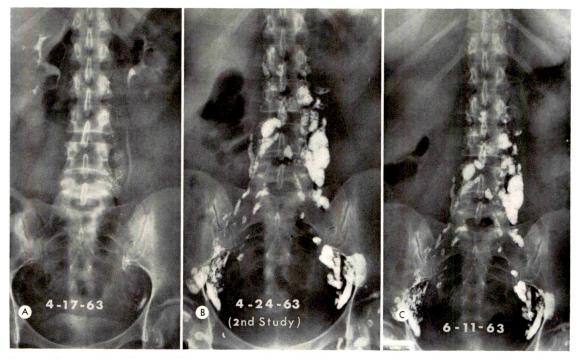


Fig. 11. Same case as shown in Figure 10, A and B. (A) Slight deviation of the left ureter and incompletely visualized retroperitoneal lymph nodes still—opacified 2 years after the first lymphangiographic study. (B) A 24 hour roentgenogram following a second injection of oily material discloses further enlargement of retroperitoneal lymph nodes, indicating recurrence of the disease. (C) Two months following radiation treatment, note the reduction in the size of the retroperitoneal lymph nodes.

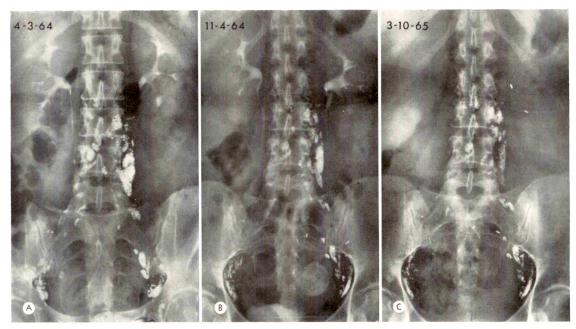


Fig. 12. (A, B and C) Same case as shown in Figure 10, A and B; and 11, A, B and C. Sequential study over a year demonstrating reduction in the size of the retroperitoneal lymph nodes and no evidence of reactivation of the disease.

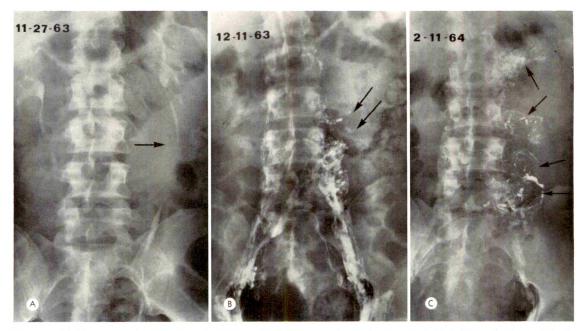


Fig. 13. Malignant testicular tumor (seminoma) with retroperitoneal metastases. (A) Note the lateral deviation of the left ureter (arrow). (B and C) Lymphangiograms disclose markedly enlarged retroperitoneal lymph nodes with signs of lymph stasis.

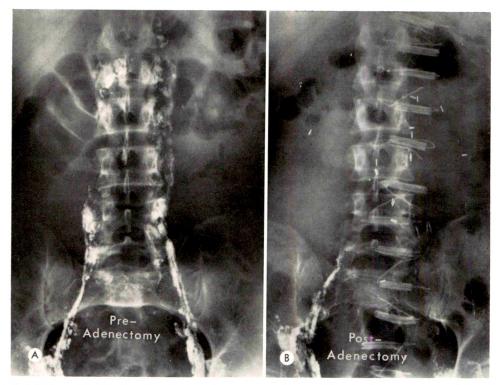


Fig. 14. (A) Before and (B) after adenectomy in a patient with a malignant testicular tumor. Note thorough adenectomy. B was obtained in the operating room and assisted the surgeon in determining the thoroughness of his adenectomy procedure.

THE EFFECT OF IRRADIATION ON THE LYMPH NODES AND LYMPH VESSELS

Some experimental studies and clinical observations⁴ tend to demonstrate that the interruption of the lymphatic flow is produced by irradiation only when the doses utilized are much greater and time of delivery much shorter than employed in conventional radiotherapy. Interruption of the lymph vessels and channels was observed experimentally only concomitant with extensive necrosis of the surrounding tissues.

Since a group of patients in this study was irradiated to the high doses estimated compatible with the tolerance of the unaffected structures, and the pelvic and paraaortic lymph nodes were included in the field of irradiation, follow-up lymphangiograms available for some of them were studied to determine the character of the lymphangiographic alterations incurred.

When no previous surgery or pelvic in-

flammatory disease preceded irradiation, even with evidence of post-irradiation reactions, no interruption of lymph flow was encountered. The most constant observation, however, was the reduction in the size of the lymph nodes. Of extreme interest is a patient who had received radiotherapy elsewhere for Stage II carcinoma of the cervix. When seen in our institution, the primary tumor appeared controlled but she complained of pain and swelling of her right lower extremity. The lymphangiographic study demonstrated lymphatic obstruction and collateral circulation at the level of the right pelvic lymph nodes. Subsequently, she was subjected to radiation therapy (5,800 rads in about 6 weeks using cobalt 60 teletherapy) to the pelvic and para-aortic lymph nodes. Radiotherapy was followed by marked subsidence of her symptoms and resolution of the edema. Lymphangiography, obtained immediately

after the described course of treatments, showed slight reduction in the size of the lymph nodes that produced the blockage but persistence of the collateral circulation already established. This case indicates that the edema of the lower extremities developing subsequent to radiotherapy of pelvic malignant tumors was probably due to persistence of the disease rather than interference of the lymph flow by the irradiation. Moreover, one of the authors administered to a dog 6,000 rads in about 5 weeks with cobalt 60 teletherapy, focal skin distance 80 cm., to the popliteal, pelvic, and retroperitoneal chain of lymph nodes. Subsequent lymphangiographic study demonstrated decrease in the size of the lymph nodes included in the field of irradiation and no interruption of the normal lymph

In spite of the known extreme radiosensitivity of the lymphoid tissue to ionizing radiations,⁸ the germinal centers affected may show regeneration but only when the dose of irradiation is low. In our experience, following a therapeutic dose of radiation, the regeneration of the follicles was not lymphangiographically detectable subsequent to treatment. This is in accordance with the findings of Taussig,¹⁰ who studied the lymph nodes of patients irradiated for carcinoma of the cervix 3 to 6 months following radiation therapy and in whom the reduced number of follicles was still apparent.

SUMMARY AND CONCLUSIONS

In a retrospective review of lymphangiograms of 201 patients with malignant diseases, it appears obvious that:

- T. Histologic-pathologic correlation in cases with squamous cell carcinoma of the genital tract often shows false positive as well as false negative findings with a tendency to over-read the lymphangiograms.
 - a. In the over-all series of 27 patients with squamous cell carcinoma of the uterine cervix in which roentgenologic and histologic correlation was obtained, there were 6 false positive and

- 3 false negative studies. Of the false positives, in 2 patients, the histopathologically positive lymph nodes were in a different location than reported by the lymphangiographer. Three false negatives had positive hypogastric lymph nodes not demonstrated roentgenographically. There were 2 cases in which histopathologically positive lymph nodes were overlooked.
- b. For more precise statistical evaluation in cases of carcinoma of the uterine cervix, a larger number of patients undergoing lymphadenectomy without irradiation would be necessary. Of interest is that clinical staging, at times, may be put in doubt by lymphangiography.
- 2. When lymphadenectomy is planned, chromolymphangiography facilitates the identification of the lymph vessels and nodes, thus allowing a more thorough dissection. Roentgenograms obtained in the operating room will verify the completeness of the adenectomy procedure. In patients with lymphangiographic evidence of para-aorticlymphnodeinvolvement,lymphadenectomy, we feel, should not be performed, and surgery should be restricted to verify the lymphangiographic findings, perhaps by a smaller incision at the level of the apparent metastases in the para-aortic region.
- 3. When a technically unsatisfactory study occurs (inadequate amount of contrast material injected, deficient radiographic evaluation), obviously correlation is not possible.
- 4. Incidental observation of this study seems to confirm that lymphadenectomy after thorough irradiation does not contribute to the survival of the patient when positive lymph nodes are encountered. The added surgery in these cases seems to increase the morbidity.⁹
- 5. When lymphangioadenography preceded thorough irradiation and subsequent lymphangiographic evaluation was per-

formed, the most constant observation was the reduction in the size of the lymph nodes within the field of irradiation.

- 6. Lymphangioadenography appeared also useful for the detection of metastatic lymphadenopathies from carcinoma of the uterine corpus; however, false positive and false negative reports may also result.
- 7. In the cases of squamous cell carcinoma of the vulva and vagina, chromolymphangiography was also useful when a radical procedure was planned.
- 8. The degree of correlation and usefulness in planning radiation therapy for malignant testicular tumors, particularly seminomas, was shown by our group of patients. Chromolymphangiography preceding planned radical pelvic exenteration, for less radiosensitive tumors of the testes, facilitates the adenectomy.
- 9. In 41 patients with various stages of lymphoma, lymphangiography proved to be of definite value in the staging and the conduction of radiation therapy and, during the follow-up period in assessing the effects of therapy on the various groups of lymph nodes included in the beam of irradiation. The degree of accuracy of lymphangiography in lymphomatous processes, when technically well performed and interpreted by experienced radiologists, approached 100 per cent.

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SYMPOSIUM ON STATISTICS*

INTRODUCTION BY THE CHAIRMAN

By A. RAVENTOS, M.D. PHILADELPHIA, PENNSYLVANIA

THE President of the American Radium Society and his Program Committee directed us to present a symposium on statistics that would be of interest to the members of this Society. Statistics is a term that has many meanings. We found it necessary to isolate a particular facet of this powerful tool of science for discussion in the time available. We have chosen to discuss only those aspects of statistical research which pertain to the selection of optimum treatment for the patient with cancer.

We will deal, then, with the sort of statistics that are used in arguments favoring one treatment method over another. According to Shimkin, this approach originated about 1834, when Pierre Charles Alexandre Louis of Paris wrote "To assure ourselves of the superiority of one or other (treatment) . . . in any disease whatever ... is doubtless to be done by inquiring if under these circumstances a greater number of individuals have been cured by one means than another." Louis named his approach the numerical method. Shimkin's excellent essay traces its vigorous subsequent development to the present day refinement of the electronic computer.

Much of our scientific literature in the field of cancer therapy is made up of such comparisons. Most of us have learned to regard them with an innate distrust, bordering on hostility, having too often seen them leaned upon "as a drunkard does on a lamp post: using them for support rather than for illumination." We have a feeling that something is wrong with many of the statistical arguments presented to us; sometimes we know what is wrong and sometimes we do not, but still know that

there is something wrong. Yet, because the words of Louis quoted above are still true, we cannot ignore or abandon this kind of research.

We try to get help from the professional statisticians. Too often, the procedure is something like this. The doctor, in the role of investigator, goes to the statistician with a poorly-defined question, and a bagful of data already collected. The doctor doesn't state the problem at all well; he leaves out all sorts of relevant assumptions and hypotheses, but avers that the data he has in hand ought to provide all the answers to the questions.

So the statistician, not really understanding the doctor's problem, solves the problem he knows how to solve. He inserts the data into some standard model or formula which gives a very precise answer replete with numerical probabilities and other esoteric terms. Unfortunately, it is the answer to a nonexistent problem.

The difficulty would appear to be one of communication between those expert in the clinical treatment of cancer and those expert in statistical reasoning. The difficulty has been overcome by a number of doctors who have learned to communicate with statisticians very effectively and by a smaller number of statisticians who have learned so much about medicine that they understand the doctor's problem better than the doctor does. We decided to bring together for this symposium an outstanding foursome of such exceptional people, 2 radiologists and 2 statisticians. It was necessary to make some territorial assignments, so that the presentation would be coherent, and the subject seemed to lend itself well to a 4 part division.

^{*} Presented at the Forty-sixth Annual Meeting of the American Radium Society, White Sulphur Springs, West Virginia, April 13-16, 1964.

I. GATHERING DATA

The first aspect to be considered is the methodology of accumulating cancer treatment data. The concept of the tumor registry to perform this function has been broadly applied for more than 40 years. Experience and critical analysis have developed the use of tumor registries to a fine art. Its present status is ably presented in the following pages of the JOURNAL by Dr. Howard Latourette.

II. REDUCING DATA

One of the many definitions that has been offered for "statistics" is "the science of reducing data." It might be very educational for a clinician to seclude himself in the vaults of the hospital records library and read several thousand patient charts, cover to cover, but this passive experience alone would not do much to make him a better doctor. Somehow, he would have to sift and sort the information, observe patterns, extract comparable facts, in other words: compile statistics. Dr. Sidney J. Cutler, an eminently qualified statistician, presented his recommendations on this aspect of methodology at the symposium. He has suggested that in lieu of a paper here, the reader be referred to the publication of the American Joint Committee on Cancer Staging and End Results Reporting.8

III. LEARNING FROM THE PAST

A great deal of retrospective data on cancer therapy is available. Its value is not to underestimate; at the same time, it is often tempting to construe too much, particularly in regard to the comparative merit of different treatments. Dr. Marvin A. Schneiderman, a statistician well-indoctrinated in medicine, became known to us through a startling little treatise entitled "Doctors Ain't So Dumb." His entertaining literary style fails to conceal the intellectual sophistication with which he treats the subject.

IV. PLANNING FOR THE FUTURE

Many of us believe that cancer therapy has a bright and promising future, not so much through the use of space-age hardware as through the use of space-age logic. The rockets were put in space by the painstaking application of a rigorous system of logic called "scientific method." It is no stranger to physicians, yet for a variety of reasons has not been applied as much in clinical medicine as might be desired. The use of the scientific method in determining the optimal treatment for cancer patients is discussed by Drs. Nickson and Glicksman.

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THE USE AND VALUE OF TUMOR REGISTRY DATA*

By HOWARD B. LATOURETTE, M.D. 10WA CITY, 10WA

HE objectives of any effort to gather or collect factual information on patients with cancer are to increase our knowledge of the natural history of cancer and to evaluate our methods of altering this natural history. Those concerned with the care of patients with various neoplastic entities are increasingly aware of their need to appreciate the basic characteristics of a particular neoplastic disease, its incidence, its behavior, and its course in different patients. Physicians trained in the use of various treatment modalities should critically appraise the survival experience of the patients they have treated. The gathering, comparison and use of these data are essential to our growing knowledge of cancer and is making us all aware of the need for more uniformity of concepts, of definitions and of classifications.

There are several distinct sources of data on patients with cancer. These sources need to be carefully identified so that the data being collected can be properly compared and evaluated. The source of data that has given us most of our knowledge in the past is that collected on individual patients by ourselves or some other physician. These data are the experience of an informed interested person or group who may publish a personal report of a series of cases. The literature is filled with these reports which reflect the degree of knowledge and ability of the authors.

Another source of information is the cooperative effort or study in which certain common terms, definitions and classifications are accepted and used in the pooling of experience. The Annual Report of the Results of Treatment of Cancer of the Uterus was one of the first such cooperative studies. The Surgical Adjuvant Breast Project is another example.

Additional sources of data on patients with cancer include those from Bureaus of Vital Statistics and from Tumor Registry Systems. This paper is concerned with the data from Tumor Registry Systems.

TUMOR REGISTRIES

Tumor Registries have been a popular symbol of a certain degree of sophistication in a hospital or medical center. They have now become a part of most so-called cancer programs and are essential for an approval of such a program by the American College of Surgeons. They now exist on a number of levels and include varying numbers of hospitals and even geographic areas. Their methods of data collection and analysis vary from simple key sort systems to those utilizing the most complex machine methods.

The numbers and varied levels and methods of operation of Tumor Registries should not prevent a periodic scrutiny of their basic value. We need to consider what benefits are derived from their function. How is the data collected being used? Are the data worth the expense? What are the limitations of these data?

In simple terms, a Tumor Registry is a collection of data on patients with cancer—a repository of information. This collection of data is of little value unless it includes facts on all the patients with "reportable neoplasms" within the institution. If any particular group of patients is not included, selective or exclusive factors are introduced that make incidence and survival experience meaningless. A Tumor Registry system usually is organized to operate in conjunction with the hospital record system and to assemble routinely certain data on each patient with cancer. Once a patient is entered on the files of a

^{*} Presented at the Forty-sixth Annual Meeting of the American Radium Society, White Sulphur Springs, West Virginia, April 13, 16, 1964. Part of the Symposium on Statistics.

Tumor Registry system, some automatic mechanism is used to gather follow-up information for a specified time interval, usually until the patient dies.

The organization of a Tumor Registry basically includes a professional director or sponsor who may have little to do with the routine function of data collection but who does represent the sponsoring group, staff or faculty. This sponsorship and interest by the professional staff are essential and their contribution can be better assured if the Tumor Registry can provide useful data. The actual collection of the data is usually done by code clerks. These individuals are record room personnel who have had considerable experience extracting material from medical records. They can be well trained to do this extraction of data according to a specific code. It is helpful to have an explanatory manual for them to follow and these manuals are gradually being developed. The code clerks are, of course, not physicians and therefore there is a distinct limitation to their ability to understand some of the reasoning that is not included in the usual hospital record. It should be pointed out, however, that they are apt to be more consistent over a period of time than varied physicians, abstracting the same material from the same records. The factual material that has been extracted from the record according to a specific code can be placed either on a punch card or on magnetic tape and stored in a variety of methods. These steps require data processing equipment and personnel. Most registries also have some type of routine follow-up procedures established. This follow-up contact is most effectively made directly with the patients and can either be done by letter or phone call. The timing of the follow-up letters and the assembling of the data from these letters vary from one Tumor Registry system to another. The basic objective, of course, is to determine the status of the patient and if nothing more than the fact that the patient is either dead or alive has been

established, it is most helpful in determining over-all survival experience.

Tumor Registry systems can exist on several different levels. The most common, of course, is a Tumor Registry within a single hospital. Such Tumor Registries should feed information back to the individuals or departments doing the treating. The manner and effectiveness of this feed-back process vary considerably. Simple Tumor Registries are now functioning in many community hospitals and somewhat more elaborate Registries are found in most teaching hospitals. Several teaching hospital registries have been collecting data for over 25 years and have helped establish the pattern for this source of information.

There are several examples in the United States of the formation of a group of Tumor Registries that pool data accumulated according to a common code and process it in a uniform manner. If the individual registries involved in this group effort completely cover a given geographic area and thereby can accumulate data on all the cancer patients of that area, significant incidence and epidemiologic data become available. Several counties in various states are now so covered and can now provide such data. The entire State of Connecticut is organized in a Tumor Registry system operating within the State Department of Health.

A national group known as the End Results Group of the National Cancer Institute has been organized to include a number of the teaching hospitals' registries and several of the state registry systems. This group has reported at the National Cancer Conferences and is compiling and publishing data indicating the over-all end results of cancer treatment across the country. This national cooperative group of registries has spent considerable time and effort trying to answer some of the basic questions regarding the value of Tumor Registry data. Our national effort to pool Tumor Registry data is paralleled in several other countries by similar systems. Several of the Scandinavian countries have excellent and amazingly complete Tumor Registry systems. There has been some attempt to compare the Tumor Registry data from various countries and this effort should have epidemiologic significance in years to come.

CATEGORIES OF INFORMATION

The general categories of information collected by most Tumor Registry systems are:

Identifying data
Date of reference
Previous treatment (if any)
Site
Histology
Stage
Treatment
Survival

The amount and detail of data in each of these categories vary according to the code used by the Registry. There is a tendency to establish originally too elaborate a code and attempt to record so much data that the record abstracting and coding cannot be kept up to date. The code needs to be relatively simple and so designed that more detailed information can be retrieved in a special study, if necessary. Certain of these categories are more difficult to code and record than others, and this fact significantly influences the possible use of tumor registry data.

The basic identifying data on a patient can be easily coded and can be used with confidence. Age, sex, perhaps some reference to socio-economic status and geographic location are the usual entries made. It has been found that the coding of race is increasingly difficult and probably is losing its significance in most parts of the country.

The date of reference is extremely important to establish. The most useful date is probably that on which treatment is started within the Tumor Registry system. Additional information in this general category may include the duration of symptomatology and the date at which the

diagnosis was established. Delays in the start of treatment due either to the patient or to the physician can be reasonably well established from such data and are part of the more elaborate codes.

It is essential to determine the previous treatment (if any) of a particular neoplasm. Primary cases are those patients in whom the first course of treatment is done within the confines of the registry system and so coded. Secondary cases are those patients in whom the first course of treatment was done elsewhere and then, usually because of a recurrence, the patient enters the institution covered by a Registry System. It is important to distinguish these two situations. In the teaching hospitals of this country, a quarter to a third of all patients entered in the Tumor Registry will have been previously treated elsewhere. This fact has considerable influence on survival data.

Site designation is difficult to code accurately in a Tumor Registry system. The categories listed in the International Classification of Disease published by the World Health Organization are a useful listing of sites of origin and are usually used in the Tumor Registry code. There are certain areas, however, in this classification that are not particularly meaningful. For example, the category "cancer of the mouth" is a most general grouping of entities and is of little value to those who actually care for lesions of the oral cavity. Accurate site designation must be done by informed physicians and recorded in the hospital record. It can then be effectively coded. Improvement of the Tumor Registry data in this category involves both professional education and improved codes.

Some reference is usually made by Tumor Registry codes to the histology of the tumor. There is, however, considerable variation in the tumor nomenclature as far as histology is concerned. The best reference for this is the manual, Tumor Nomenclature in Coding, The American Cancer Society, 1951. Before a great deal of uniformity of these data can exist in Tumor

Registry systems, there must be more agreement among the pathologists themselves.

Staging of a malignant neoplasm implies some attempt to record the extent of the tumor. It has been found by the experienced registries that perhaps all that can be used in this category are the general classifications of "localized," "regional" or "distant." The "localized" designation implies that when the patient was first entered into the Registry system, the tumor was confined to the site of origin. "Regional" spread would be that there had been extension of the tumor from the site of origin into regional structures or that regional lymph nodes were involved. The definition of regional lymph nodes, of course, varies somewhat and there is possibility of considerable varied individual interpretation in this category. "Distant" spread refers to organs involved at some distance from the site of origin. More definite staging schemes, of course, have been devised. The American Joint Committee's attempt to describe the extent of a neoplasm according to the TNM system is gaining increasing popularity. Much has to be learned regarding the applicability of such schemes and when these are generally accepted by the medical profession, they then can be incorporated into the Tumor Registry codes. It is difficult for Tumor Registry clerks to go through a hospital record and try to establish the exact stage of a neoplasm when little is done in this regard by the physicians creating the hospital record. An important consideration in staging is whether or not the information that is used is entirely clinical or whether it involves information available as the result of the first course of treatment. This would then include the information available after a surgical procedure which had been used as a therapeutic attempt. It is important to distinguish clinical staging schemes from those that involve the information available from surgical therapeutic procedures and the evaluation of a surgical specimen by the

pathologist. In any attempt to evaluate treatment, this needs to be considered because the refinement of staging that is possible using surgical treatment modalities is not possible using radiotherapeutic techniques.

The recording of data on treatment using Tumor Registry methodology must be limited. Those abstracting medical records are able to record the general type of treatment but cannot be expected to evaluate the details of treatment accurately or consistently. Likewise, it is very difficult to include in Tumor Registry mechanisms proper evaluation of the factors influencing the selection for a particular treatment modality. It has been determined by experience of the End Results Group that the general categories, "surgery, radiation, surgery plus radiation, no treatment, and other," are as far as a Tumor Registry code can be extended. Likewise, it is impossible to accurately list and record the morbidity and mortality associated with various treatment modalities.

The general category of information on survival is relatively easily and accurately provided by a Tumor Registry system. A mechanism can be established so that every patient in the Tumor Registry files is contacted regularly after treatment is completed. This information can be added to the individual hospital record and also assembled by machine methods to provide information on over-all survival experience. The factual information may only be that the patient is either alive or dead but over a period of time this information is most valuable. These survival data can be processed and presented in many different ways.

CAREFUL EVALUATION OF THE DATA

These basic limitations involving the recording of site, stage, and treatment details make necessary a careful evaluation of the data gained from Tumor Registries; they make it unreasonable to be too elaborate in the data processing and to expect from the massive data being col-

lected refined details. Likewise, it is incorrect to try to compare data too closely. When data involve large numbers of patients, which is one of the characteristics associated with this source of data, there is a natural impulse to try to use it to evaluate treatment modalities. As has already been indicated, this type of use of Tumor Registry data must be very carefully done. When it is impossible to determine site, stage and treatment details accurately, it is impossible to critically evaluate treatment modalities. This is true particularly in the comparison of the results from surgery as opposed to radiation therapy. Clinical trials can provide much more accurate data of this nature.

THE USE AND VALUE OF TUMOR REGISTRIES

The structure and function of Tumor Registry systems have been described and the nature and limitations of the data so collected have been outlined. Bearing this in mind, what then is the use and value of the data? Is it worth the over-all effort and expense to maintain a Tumor Registry? The answers to these basic questions vary with individual and group opinions. The effort necessary to operate a good Tumor Registry has a distinct educational influence upon the professional staff of an institution and the data collected have a number of uses. The current consensus of opinion is that the total effort to collect information on cancer cases in this manner is worthwhile.

As a source of information on the over-all end results of treatment of cancer at an institution or for a group of institutions, Tumor Registry data are valuable. It provides the best data we have on relatively large numbers of patients. The End Results Group has data available for analysis on almost 500,000 patients with various types of neoplasms. This is a unique source of such data and can provide a necessary baseline of information, particularly, on over-all survival for many special more detailed studies. The feed-

back of such information to the contributing institutions is an educational effort that needs to be emphasized. Making the medical profession more aware of over-all survival results is one of the values of a Tumor Registry system.

Because of the relatively large numbers of patients involved, Tumor Registry data can be used to gain some degree of understanding of the natural history of certain neoplasms. It is possible for instance to go to Tumor Registry data for the over-all survival experience of untreated bronchial carcinoma and to use that information to help to establish some baseline against which to evaluate attempts to alter that natural history.

The use of machine methods makes it simple to compare Tumor Registry data over various periods of time. In this way, trends can be demonstrated. Changes in the incidence, age, distribution of various neoplasms can be shown as well as those relating to our educational efforts of the public so that more localized lesions are seen and treated. Trends involving treatment modalities and, most important, survival can be easily provided from Tumor Registry data. Machine methods can be used to evaluate several different variables using relatively large numbers of patients. These variables could include stage, treatment modality, survival and time period. In some neoplastic entities, there has been remarkably little improvement in survival over a considerable period of time as is well known. In other sites, neoplasms have been relatively poorly handled in the reporting institutions covered by the Tumor Registry systems when the survival experience is compared with that reported in specialized or personal studies. This type of comparison lends some increased understanding to the total problem of our care of patients with målignant neoplasms.

The studying of Tumor Registry data does make possible or suggest more detailed studies. A pooling of information covering large numbers of individuals makes possible some increased understanding of relatively rare tumors. The association of various types of malignancies can be suggested and partially evaluated using Tumor Registry data. The ultimate cause of death and what factors are involved in the selection of treatment modalities are other special studies that might well be suggested by an analysis of the relatively crude data coming in from Tumor Registry systems.

The survival experience of an institution's Tumor Registry population can provide very valuable information to individual departments or physicians who are trying to maintain more detailed records of the accomplishments of their treatment. Certainly, every physician who spends much of his time treating patients with cancer is aware of the need of a constantly up to date system to provide him with information on his current rate of accomplishment in his endeavors. Tumor Registry data can be fed into this more refined detailed individual study in a rather effective manner. It is my personal opinion that this is one of the chief values that a Tumor Registry system might have.

The analysis of Tumor Registry data may well suggest epidemiologic studies. The comparisons of incidences and types of tumors from various population groups across the country or across the world can be appreciated using Tumor Registry methodology. Such epidemiologic studies then might well follow.

The evaluation of treatment modalities is difficult because of the number of variables involved. The techniques of treatment, the individual variation of neoplasms, the variation in natural history, as well as the ability of the physicians involved, all are difficult to ascertain and code in a Tumor Registry mechanism. Clinical trials are essential for the careful evaluation of modalities whose results are quite close numerically. Certainly, this type of careful evaluation is not possible using Tumor Registry data.

CONCLUSION

Tumor Registry data have distinct limitations and very definite uses. The use varies with the operational level of the Tumor Registry. The attempt to utilize Tumor Registry data emphasizes the need for uniformity of concepts, definitions and of classifications. The use of these data is markedly increased if they can be studied and evaluated by informed individuals who can apply the relatively crude information obtained in this manner to more careful studies.

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LOOKING BACKWARD: IS IT WORTH THE CRICK IN THE NECK? OR: PITFALLS IN USING RETROSPECTIVE DATA*

By MARVIN A. SCHNEIDERMAN, Ph.D.†
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"And all our yesterdays have lighted fools the way to dusty death."

Shakespeare (Macbeth)

NoT long ago I found myself a minority of one objecting to a Junior High School "Science" program. My objection was that they were using living materials, in an insensitive way, to learn what was already quite well known. The reply to my objection was that the students needed to be taught how to manipulate the materials of science (i.e., mice, hamsters, etc.)—and this they were getting. I felt that while they were manipulating mice and hamsters they were not learning to manipulate the literature, perhaps the most important of the "materials of science."

To me "the literature" is the history of what has been done in the field. It contains lots of data. Since we look back on it, it becomes "retrospective." However, just as a misplaced reliance on manipulating materials (or on developing "original" data) can lead to anything from foolishness to a lack of respect for life, the excessive reliance on the literature can also lead to gross and subtle errors. Hence, this paper on pitfalls in using retrospective data.

The clinician learns through his own extensive experience—and a little from the experience of others. I say "a little," because I believe that much of the clinician's learning is kinesthetic, in which he incorporates things and ideas into himself unconsciously. This learning is like learning how to swim or ski. Someone else can tell you what to do to help you learn, but the learning itself is all your own. Since this learning is individual, we should not be surprised to find people differing—some-

times vigorously—when they pit "In my experience..." against each other. There's nothing wrong with a man's citing his experience. In fact talking about "in my experience..." is a forthright way of referring to one's personal literature—in gentlemanly contrast to the "documented" reference for that surprising finding that turns out to be a "personal communication,"—available only to the author.

While the statistician will warn about the pitfalls of using history, especially personal history, he is not bound by oath to be opposed to using retrospective data. There is, in fact, a substantial, respectable, fairly old field of statistics that bases today's decisions on yesterday's (and older) data. This is the field of Quality Control worming its way into clinical pathology). Here, past averages and past variability are used as a basis for determining whether current operations are "in control," i.e., if they conform to the past. There is now even a small-scale ("Bayesian") revolution going on in the field of statistical inference by people who are attempting to use history in a formal way to help assess the results of current experimentation.

If statisticians can use retrospective data in their own field, why do they object when other people use it in theirs? In part, I believe some of the difficulties are derived from retrospective data which are only one man's experience. Since (most of the time) each man's experience is different from every other man's, we must expect dif-

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ferent conclusions, when the test of experience is applied. How much, then, are we to trust experience? And whose? And is what we are working on today really comparable in all pertinent respects with the case history series with which we wish to contrast it?

Thus one meaning of the word "retrospective" is the literature, both formal and informal. One should also consider the word in a different, perhaps more technical, sense. The word "retrospective" is used technically in contrast to the word "prospective." If a prospective (looking forward) study starts with a group of people with defined characteristics and one follows them in time to see how they sort themselves out, the retrospective study starts with them already sorted out (i.e., women with cervical cancer and women not with cervical cancer) and one tries to go back to find what defined characteristics may have led to the eventual sorting-out (was it age, number of pregnancies, use of synthetic estrogens?).

In the absolute, there is no theoretically superior virtue to one form of study over the other. Any real superiority lies in one approach being less prone to errors and relying on fewer unverifiable assumptions than the other. In studying health phenomena, what one usually finds is that an unusual sorting out has occurred (i.e., some people have cholera and some don't). We have an idea of what may be a prior condition that led to this sorting out (is the drinking water polluted?): We gather evidence by looking back into the history of each individual in the two groups, which may provide a partial test of this idea, and in so doing—we have done a retrospective study. In the public health field this is often the only kind of study that can be done. Usually it has to be followed by a prospective study as a further test.4 The suspected causal agent must be removed from the environment, and we observe whether the incidence of new cases falls off compared to the history.

In the last stage of this retrospective

TABLE I

User	Dis	ease	
of Drug	Yes (+)	No (-)	Sum
Yes (+)	a	ь	a+b
No (-)	С	d	c+d
Sum	a+c	b+d	a+b+c+d=N

study, there are difficulties and potential sources of error. First, the conceptual one. Say we wanted to find if there were a relationship between cervical cancer and the prior use of synthetic estrogens. Since this is a retrospective study we start with two populations of women, one with cervical cancer and one without. We then find if the members of these populations were, or were not, users of a synthetic estrogen. The resultant data are given in Table I, where a, b, c, d are the numbers of persons who fall into each category. Now we compare

$$\frac{a}{a+c}$$
 with $\frac{b}{b+d}$.

This comparison raises the question: "Is the proportion of drug users the same among women with cervical cancer as among women who do not have cervical cancer?" Notice this question. It is about drug use among diseased persons—not about disease among drug users. It has to be that way, because our basic sample was of persons chosen with respect to disease—not with respect to drug use. This is a "backwards" question. We really want to know the other thing, disease among drug users.

Some arithmetic manipulations, coupled with a set of innocuous-appearing assumptions can lead to an inversion of the question—eventually allowing us to ask about

$$\frac{a}{a+b}$$
 compared with $\frac{c}{c+d}$.

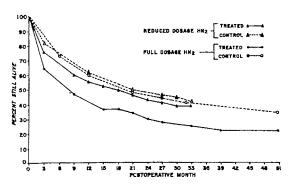


Fig. 1. Percentage survival of patients with lung cancer treated postoperatively with full and reduced dosage of NH₂. The curves represent 1 month survivors still alive at successive 3 month intervals up to January 15, 1962. (Reproduced with permission of authors and the Journal of Thoracic and Cardiovascular Surgery.)

The ratio of these two is the "relative risk." The arithmetic manipulation raises no problems. Fulfilling the assumptions usually does. First, we must assume that it is possible to "enumerate all...cases of a disease, or a representative sample of them..." Since we almost never are able to enumerate all cases, we almost always find ourselves with a sample. Is it "representative?" What constitutes a representative sample? All the patients in one man's practice? All the patients in one hospital? In several hospitals? What is this sample representative of?

One also needs a representative sample of the non-disease population. Where does one get this? Other patients with different diseases? Normals? Who are they? Do we need the same proportion of all the non-disease persons in our sample as we have of the "disease" persons? What about a rare disease? If we need 100 cases of the disease in order to be able to draw valid conclusions and this is half of all new cases reported in a year, surely we don't need half of the non-disease population as our sample. But what per cent will we need? Some people try to get two controls for every case. Is this enough? Too much?

Some classic errors have been made by

the mis-selection of the "control" population. Selection of the wrong control population will lead to bias—wrong answers. If we were to really do the cervical cancersynthetic estrogen study, what would be a good control group for the cancer patients? At least age, social class, number of pregnancies, and several of the other factors that have been reported as related to cervical cancer might have to be taken into account.

There are other problems of bias. If the investigator believes, for example, that the use of the synthetic estrogen is predisposing to cancer of the cervix, is he more likely to press the cancer patients for an affirmative answer about their use than the "control" cases? Moore8 suggests some other possible after-the-fact biases which one may introduce. Here are two examples: "Techniques for excluding uncooperative patients from follow-up . . . have been perfected;" and "Your 'batting average' in neck dissection is greatly aided by including as many small cancers of the lip, face, and buccal surface as possible and omitting 'undifferentiated' cancers of the tongue.'

Next there are memory biases—or just plain not-knowing. For example, I have twins. When my father proudly announced their birth to his oldest brother, he added, "You know, I think these are the only twins in our family." To this his brother replied in surprise, "That's not so. Didn't you know that Pop was a twin-and that his twin brother died in infancy?" Clearly before the birth of my twins I would have given a different answer to the question "Was any of your grandparents a twin?" than I would have a few weeks after. People with a disease, or special condition in their immediate family are probably much more conscious of another relative who "had it," too.

Several examples follow of work in which the question could arise as to what case history data might mean. I cite these not for their substantiative importance but for the light they may throw on the methodologic issues involved in using such data.

Figure 17 illustrates survival in a carefully controlled study in which patients were treated by surgery or by surgery plus HN₂ as an adjuvant, for lung cancer. After a number of patients had been admitted, it was feared that the dose of HN2 was too high, and the dose was lowered for the second part. Randomly assigned nonadjuvant-treated controls were included in both parts. The survival curves for the two parts show a clear dose-response relationship—the patients on the smaller dose behave more like the controls. Did one really need the second set of controls? Would one have been misled if there had been only the first set of controls? Probably not. Could one have known this in advance? (The figure is correct. Treated patients did more poorly than their controls.)

Figure 2 is from a study of surgery and chemical adjuvant therapy in the treatment of breast cancer. The situation here was similar to the one described above. After an initial group of patients had been admitted, the dose of the adjuvant was reduced and a second controlled study was done. The figure shows probability of re-

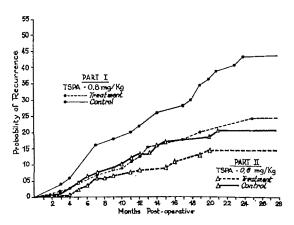


Fig. 2. Probability of recurrence in breast cancer treated with surgery and postoperative high dose (Part I) and lower dose (Part II) TSPA. (Reproduced with permission of the author and the *Annals of Surgery*.⁹)

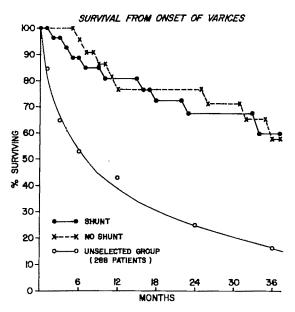


Fig. 3 Percentage survival from onset of varices in a controlled trial of prophylactic portacaval shunt surgery. (Reproduced with permission of the authors and the New England Journal of Medicine.⁵)

currence with passage of time. In the first (high-dose) series, the treated group appears to have done better than the control group. This also seems to be the case for the second (lower-dose) series. The difference between treated and controls appears smaller, where the dose was smallerwhich is reasonable. But, suppose that there had not been a second control series. and the authors had relied on the first control series alone. Then the lower dose (second series) would appear to have had a greater beneficial effect than the higher dose. Either one would have to dismiss this or else one would have to do many further experiments to find the optimal dose. However, there was also a concurrent control in the second trial, and the smaller treatedcontrol difference is in keeping with a reasonable dose-response relationship. It appears as if the whole group of patients was different in the second series. Thus the second group of control patients was not only not "wasted," but provided substantial additional information and pre-

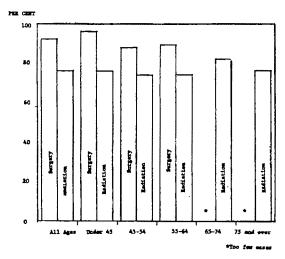


Fig. 4. Percentage 5 year relative survival by initial treatment and age in localized cancer of the uterine cervix. (Reproduced with permission of the authors and the National Cancer Institute Monographs.*)

vented a potential misinterpretation. Relying on case history controls here would have given the wrong answer.

Figure 3 shows a related phenomenon. Here the problem was whether one could compare the results of prophylactic surgery with the results in an unselected group of patients, or was it mandatory to designate, in advance of treatment, which patients were to be compared? The answer is clear. The mandatory pre-designation was essential. The "treated" patients and their proper controls (two top lines) are very close in their responses. The "unselected patients" did far worse. It would almost appear as if the mere selection of a patient to participate in this studywhether he was treated or not, substantially improved his chances.

The last figure, Figure 4, is a graphic presentation of data compiled by Cutler and Ederer.³ These are case history data from cancer registries. If one trusts these results implicitly, it is obvious that the proper treatment for localized cancer of the uterine cervix is surgery. But one has no assurance that the surgically treated patients in this series differ from the

radiation treated patients only in the modality of treatment. Why was surgery chosen for one, and radiation for another? Surely, there must have been some reason. I contend that these data are a good example of a place to apply the proscription of Dr. Latourette "Data from registries must be applied with caution." I would probably make it stronger. I would say that the surgery-radiation controversy presented here can probably be resolved only by a controlled trial, as discussed by Drs. Nickson and Glicksman in their part of the symposium.

At this point, I fall back upon my favorite Mathematician¹ and report the Oueen's advice to Alice:*

"Consider what a great girl you are Consider what a long way you've come Consider what o'clock it is Consider everything."

If you do, you can probably do retrospective studies successfully. Despite much cynical citing of Murphy's law, because an error can be made, does not mean that it will be made. Retrospective studies can be conducted well. Prospective studies can probably be done better.

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^{*}To my knowledge, Professor Donald Reid of the London School of Hygiene first suggested applying this advice for practitioners of the controlled clinical trial.

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CLINICAL TRIALS IN RADIATION THERAPY*

AN APPLICATION OF STATISTICAL METHODS TO CLINICAL RESEARCH

By JAMES J. NICKSON, M.D., and ARVIN S. GLICKSMAN, M.D. NEW YORK, NEW YORK

IT IS the purpose of the authors to review the present methods of making decisions about the relative merits of different methods of treatment and to discuss the application of statistical techniques to clinical research in the form of clinical trials. There is a growing awareness on the part of the medical profession that our usual means for making these judgments are not precise and may lead us astray. We need to know whether or not any difference in results follows the use of varying methods of treatment when applied to comparable patients. At present, with few exceptions, we continue to rely upon the judgments of those in positions of authority. The use of properly designed clinical trials permits us to move from an authoritative frame of reference to a scientific one.

Past experience constitutes one of the major bases of forming judgments of the value of treatment. The most primitive level is the recall of the response of a few patients, and this activity has received a variety of names; "serendipity" and "anecdotal research" are among them. Another way of asking questions of the past is to review the experience of the department or institution and to form judgments based on the behavior of large numbers of patients. For many years this has been the primary method of evaluating differing treatments. It may still be a worthwhile endeavor. The usefulness and limitations of this procedure are discussed by Schneiderman.²⁰

Today it is insufficient to continue to use analysis of past data as the sole or even major basis for making firm decisions about policies of treatment. This is so, first, be-

cause an inherent assumption is made that there has been no variation of patient material as a function of time or that, if such variation exists, its extent can be assessed and taken into account in analyzing the results. In other contexts, we are used to the idea that our patients change. Much has been made of the importance of early diagnosis. In fact, patients with many kinds of cancer now appear for treatment with an earlier stage of the disease. There are numerous studies in the literature with regard to carcinoma of the breast19 and carcinoma of the cervix,8 which show or purport to show that patients are appearing with earlier disease than formerly was the case. However, we tend to ignore or forget this possibility when we are considering the consequences of treatment.

We should also be aware that the patients we see with a particular disease represent only a portion of the total population with that disease; but we have no way of ascertaining the relationship of our patients to the entire population. Changes in public attitudes, mores, and education alter the percentage of total population with cancer which appear at the hospital for treatment. While one may be getting patients with a somewhat earlier stage of disease, one may also be getting different proportions of aggressive versus indolent cases. One hundred or even 50 years ago, only the most virulent and troublesome cases appeared for treatment. With dissemination of medical information and improvement in diagnostic techniques, the less aggressive, uncomplicated cases, whose natural history may be completely different from that of the previ-

^{*} Presented at the Forty-sixth Annual Meeting of the American Radium Society, White Sulfur Springs, West Virginia, April 13-16, 1964. Part of the Symposium on Statistics.

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ous group, appear. To the degree that the population basis is changing and to the degree that we forget or ignore this fact, our judgment may be wrong about the effectiveness of current treatment policies. For example, if we change on the first of a given calendar year and do things differently for 5 years and then compare our results with those in the 5 year segment prior to the date of change, we might conclude that our new treatment is better than the old one. The results may be better but because of change in the patients, not a more effective treatment.

Another sort of change as a function of time has to do with the quality of care given by the physician. A slow but steady improvement in the results may be seen without a change in treatment plans due to greater skill on the part of the physicians applying a stable policy of treatment. Heyman⁵ emphasized this very well concerning the treatment of carcinoma of the corpus uteri. In his own series his results steadily improved. Heyman believes that a considerable portion of the improvement was due simply to his greater skill in applying the treatment and his greater skill in the management and prevention of morbidity and mortality.

A third consideration is changes in our ability to deal with untoward effects and with complicating medical problems. These have improved steadily with time. The application of physiologic methods to patient care, the understanding of the metabolic responses of patients to trauma and the use of suitable antibiotics have a favorable influence on survival rates even if the policy of treatment is unaltered.

Another commonly used method of accumulating information is to compare published results based on past experience from different institutions. This is a hazardous and frequently meaningless exercise. Where sharp differences are found, discussions commonly develop with regard to the comparability of material. International committees have set up standards and staging criteria, but even so,

the person with the apparently poorer results maintains with considerable vigor that the quality of his material is responsible. This may, in fact, be the case. Alternatively, it may be argued that the disease in one country is different from that in another country and that this accounts for the difference in the results. A third consideration diminishing the value of interinstitution comparison is the criteria for pathologic diagnosis. Ancillary measures such as supportive care and laboratory investigation will also vary.

In some instances, it is possible to accumulate useful information retrospectively about tumor behavior and response to treatment by setting up international panels which review the pathology and the clinical data on each case. This technique has been most applicable to rare tumors such as thymoma but unfortunately is impractical for the commoner cancers; e.g., carcinoma of the lung.

This list could be extended, but it is hoped that the examples have been sufficient to convince the reader that it is improper, unscientific and intellectually fattening to fail to have, whenever possible, controls contiguous in time and place with the trial group and to assign patients randomly to methods of therapy to be compared. It is today the only way known whereby one can attempt to control these and other variables in patients being treated and ensure as best one can that if a difference in survival emerges it is probably due to the alternative treatments being compared. What is needed then is the application of valid statistical methods to clinical research.

Physicians in many contexts have had increasing contact with the laboratory and have become aware of the application of statistical methods to biologic problems and now to clinical problems. The application of this discipline to the gathering of information is now acknowledged to be a powerful aid in arriving at decisions with regard to the treatment of patients with cancer.

What, then, is a clinical trial? Hill⁶ has stated, "The clinical trial is a carefully and ethically designed experiment with the aim of answering one precisely framed question. In its most vigorous form, it demands equivalent groups of patients concurrently treated in different ways. These groups are constructed by the random allocation of patients to one or another treatment."

The first and in some ways the hardest problem is deciding upon the question you wish to answer. Commonly, in radiation therapy this involves a question with regard to the relative value of two forms of treatment. The question may involve comparisons of two alternative modes of treatment, such as irradiation and surgery, or it may involve one kind of treatment compared with combinations of two or more other forms of treatment. Many examples can be given of important questions. Is the classic Halsted radical mastectomy better, the same, or worse than simple mastectomy combined with radiotherapy as proposed by McWhirter? The evidence at hand consists solely of information from different institutions. Since no information exists as to the comparability of the material, the data have provided and continue to provide a basis for heated arguments rather than for making decisions. Unless and until a properly designed randomized clinical trial is performed, we will not and probably cannot pass on to other questions. Kaae and Johansen⁷ report on a properly designed clinical study comparing an extended radical mastectomy with simple mastectomy and radical radiotherapy. These patients all came from the same institution, were handled by the same surgeons and the same radiotherapists, and were assigned randomly to the groups after being staged jointly. Their results would indicate that there is very little difference between the two methods of treatment in their institu-

Radium plus roentgen-ray therapy is the standard treatment for carcinoma of the cervix. Recently, Paterson and Russell¹⁶ designed a clinical trial to determine

whether any difference in the results occurred if radium preceded external therapy or vice versa. The evidence fairly well indicated that x-ray therapy *before* radium was better than x-ray therapy *after* radium, particularly for Stage III cases.

Interest has developed recently with regard to the combined sequential application and surgery in the management of a variety of cancers. Randomized clinical trials are now in progress in many institutions which hold a fair probability of producing a reasonable answer as to whether either radiological or surgical treatment when used alone is better, the same, or worse than combined sequential application of irradiation and surgery.⁴

What other considerations underlie a decision to establish a clinical trial? Clearly, past experience constitutes one of the major ways this comes about. On occasion, it may be sufficient to recall the response to treatment of one or of a few patients. The use of this kind of observation and cesign for future prospective trials depends heavily upon the wisdom and judgment of the observer. The insight of great clinicians in the past has contributed impressive bases for many studies. On the other hand, it has also been the cause of a great deal of controversy when factors unappreciated at the time of the observations invalidated the universality of the observations.

A logical consequence of consideration of the past is the setting up of a pilot study. This is designed to accumulate in an orderly manner further observations on a small number of comparable cases. One gains an impression of the rate at which cases can be accumulated; the principal problems of the therapeutic modalities to be tested may become apparent; and some idea of the kinds of relevant observations that should be made on all patients can be foreseen. From this, a reasonably well designed prospective clinical trial can be organized.

The differences between alternative methods of treatment of patients with cancer are relatively small, usually. Should

a method of treating cancer emerge which doubles the salvage rate, there would be little or no need for elaborate studies to detect this. The design of experiments to look for small but clinically worthwhile differences is, however, extremely difficult and requires the advice and cooperation of a statistician at the initiation and design as well as in the interpretation of the results of a clinical trial.

A clinical trial should be considered if, and only if, an honest question exists concerning the management of a particular disease. This uncertainty means that the medical profession must examine the problem with the most valid scientific methods. Ethically, we are obligated in discharging our duty as physicians to undertake these investigations on human subjects whenever acceptable alternative methods do not exist. Claude Bernard, one of the originators of modern experimental medicine, summarized the situation thus: "Among the experiments that may be tried on man, those that can only harm are forbidden; those that are innocent are permissible; and, those that may do good are obligatory."

Generally, it is agreed that the doctor should obtain the patient's freely given consent after the patient has been given a full explanation.2 However, in dealing with the management of patients with cancer, it is not always feasible to explain in detail to the patients the basis for the uncertainties of various therapeutic techniques without disturbing the patients' confidence and without producing severe psychologic problems. In a statement by the Medical Research Council of Great Britain on the responsibility in investigations on human subjects, it is pointed out that whenever possible the true consent of the patient should be obtained. "Occasionally, however, to do so is contraindicated. For example, to awaken patients with a possibly fatal illness to the existence of such doubts about effective treatment may not always be in their best interest." In this setting the ethical responsibility of the doctors undertaking the clinical trial is that much greater. "A blind adherence to an inflexible code may be unrealistic, but an honestly cultivated sense of ethics should point to the right course." We believe this statement appearing in the New England Journal of Medicine best summarizes the ethics of investigations on human subjects.

This paper is designed primarily to persuade the reader that clinical trials represent a better way of collecting information upon which to base decisions about treatment policies. For those who have been persuaded and wish to seek information about how to proceed, they cannot do better than refer to Mainland's excellent text.¹⁰ Although there are many texts addressing themselves to this question, Mainland's has the immense merit for us of being written by a physician who has become acquainted with the complexities of design of clinical trials. Thus, it is written from the point of view of the physician and from the point of view of a person in statistics.

The bibliography lists some references not mentioned in the text.^{1,3,9,:1-15} These are cited to permit the reader to review further examples of well-designed, well-executed studies involving treatment with ionizing radiation of patients with cancer.

In conclusion, the philosophic basis of clinical trials is best summarized by Professor Paterson in referring to work at the Christie Hospital and Holt Radium Institute concerning randomized clinical trials involving patients with cancer of the cervix... "The first is that there are for, I think, the first time in the history of radiotherapy truly objective and scientific studies not in any way dependent on personal bias and so of very different value as evidence from our previous approaches to the numerous problems which confront us in evolving technique.

"The second is that in the present state of our knowledge the policies indicated as better by the results of such clinical trials must be regarded as superior and likely to be to the patient's advantage. "The term 'Clinical Trial' is used in the United Kingdom in reference to controlled comparative studies involving patients. They have to employ as rigid a scientific discipline as any laboratory experiment. Their use has greatly advanced our understanding of tuberculosis, rheumatism, and heart disease. Application to malignant disease is more difficult... Nevertheless such experiments are entirely possible and ethical and prove most informative, often surprisingly so." 17

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THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

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M EDITORIAL M

THE FORTY-EIGHTH ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

THE Forty-eighth Annual Meeting of the American Radium Society will be held at the Camelback Inn, Phoenix, Arizona, April 13–16, 1966.

The Society will celebrate its Fiftieth Anniversary at this meeting. Dr. Edith H. Quimby has compiled a great deal of interesting data concerning the history of this Society which she will present to the members and guests on Friday, April 15, 1966.

The membership of the Society is comprised predominantly of radiotherapists, cancer surgeons and radiation physicists. All physicians and allied scientists interested in the diagnosis, treatment and research of cancer are welcome. They should apply directly to the Camelback Inn for reservations specifying that they will be attending the Annual Meeting of the American Radium Society.

The Tentative Scientific Program and Schedule of Events appear elsewhere in this issue of the JOURNAL. Fifty papers will be presented dealing with a great many facets of the cancer problem.

Dr. Charles Botstein has organized an outstanding symposium concerning the advantages and disadvantages of electron beam therapy.

Our distinguished foreign guests will include Dr. Adolph Zuppinger of Bern, Switzerland, Dr. Maurice Tubiana of the Institut Gustav Roussy, Villejuif, Seine, France, Miss Margaret D. Snelling, F.R.C.S., F.F.R., President of the British Institute of Radiology, Dr. M. Lederman and Dr. Vera M. Dalley of the Royal Marsden Hospital, London, England. These physicians will participate in the symposia

or deliver essays on subjects of their choice.

Dr. W. R. Bruce of Canada will present the results of studies of the action of chemotherapeutic agents at the cellular level. Dr. Leo G. Rigler will discuss the search for hidden cancer. Dr. Zuppinger will present his views on the treatment of patients with osteogenic and soft tissue sarcomas. Radiation and the epidemiology of cancer will be discussed by Dr. Lester Breslow. The application of newer radiation biology knowledge to radiation therapy will be presented by Dr. Maurice Tubiana. Dr. R. Lee Clark, Jr., the Director and Surgeon-in-Chief of the M.D. Anderson Hospital, will discuss the present and future status of cancer therapy.

There are so many outstanding essays that it is not possible to call attention to each one. It can only be stated that no one interested in the management of the patient with cancer can afford not to attend this meeting.

The Camelback Inn is located II miles from Phoenix and 4 miles from a most delightful shopping center located in Scottsdale. The usual winter temperature varies from 70 to 80 degrees by day and 40 to 50 degrees by night. The deluxe guest rooms are located in 30 "casas" (Spanish for houses) which have from 3 to 10 rooms each. The Inn is situated on 241 acres. Arizona's finest golf course is located very close to the Inn.

Swimming, horseback riding, hiking, pack trips, tennis, pitch and putt golf course, and dancing are available.

The Scientific Program will be held between 9:00 A.M. and 1:00 P.M. daily, leaving the afternoons free for the members

and guests to enjoy the opportunities afforded by this location.

With his Committee Members, Dr. R. Lee Foster of Phoenix, the Chairman of the Local Arrangements Committee, has arranged an outstanding Social Program. There will be a chuck wagon barbecue in the evening on the desert. The Annual Banquet will be held beside the swimming pool. Excellent entertainment has been arranged.

The Janeway Lecture, an outstanding event of the Annual Meeting, will be delivered by Dr. Gordon P. McNeer, Associate Professor of Clinical Surgery, Cornell University Medical College; Attending Surgeon, Memorial Hospital for Cancer and Allied Diseases, New York, New York. The title of his lecture will be "The Problem of the Local Recurrence of Malignant Melanoma."

Registration will start at 12:∞ NOON on April 12, 1966 at the Camelback Inn.

Application forms for reservations will be mailed to all members of the Society and they should be returned promptly to the Camelback Inn in order that both the hotel and the Arrangements Committee may anticipate the number of registrants as far in advance of the meeting as possible. Registration will be automatic upon the receipt of your confirmed reservation inasmuch as the Arrangements Committee will receive a copy of each reservation from the hotel. Scientific Guests will be charged a nominal registration fee.

The Officers of the American Radium Society cordially invite you to attend the Forty-eighth Annual Meeting and to help celebrate the Fiftieth Anniversary of this Society.

Justin J. Stein, M.D. President, American Radium Society

UCLA Center for the Health Sciences Los Angeles, California 90024



THE AMERICAN RADIUM SOCIETY

PRELIMINARY PROGRAM

The following is the preliminary program arranged by the Scientific Program Committee for the Forty-eighth Annual Meeting of the American Radium Society to be held at the Camelback Inn, Phoenix, Arizona, April 13–16, 1966.

Tuesday, April 12, 1966

9: O A.M.—4: O P.M. Executive Committee Meeting. 12: O NOON—6: O P.M. Registration.

Wednesday, April 13, 1966

8:∞ A.M.—4:∞ P.M. Registration.

9:00 A.M.

Opening Ceremonies and Welcome Address, Forty-eighth Annual Meeting.

Governor Sam Goddard, State of Arizona.

James E. O'Hare, M.D., President, Arizona Medical Association, Tucson, Arizona.

9:10 A.M.

The President's Address—Justin J. Stein, M.D., President, American Radium Society, University of California Center for the Health Sciences, Los Angeles, California.

FIRST SCIENTIFIC SESSION
Manuel Garcia, M.D., Chairman.
Charity Hospital of Louisiana, New Orleans,

9:20 A.M.

Louisiana.

The Present Status of Mammography and Training Program. Wendell G. Scott, M.D., St. Louis, Missouri.

9:40 A.M.

Mucosal Melanomas of the Head and Neck. Daniel Catlin, M.D., Memorial Hospital, New York, New York.

9:55 A.M.

The Place of Arteriography in the Diagnosis of Cancer. W. A. Weidner, M.D.,* UCLA Center for the Health Sciences, Los Angeles, California. 10:10 A.M.

Experience with Iridium 192 Ribbons with Particular Reference to Radical Neck Implants. James W. Rowe, M.D.,* James Fischer, M.D.,* Yung H. Son, M.D.,* and Carl F. von Essen, M.D., Yale University School of Medicine, New Haven, Connecticut.

10:25 A.M.

Therapeutic Integration of Breast Cancer. German Garcia, M.D., and Isabel Algorri, M.D.,* Spanish Hospital, México, D.F., México.

10:40 A.M.

Does Prophylactic Radiotherapy Given for Cancer of the Breast Predispose to Metastasis?

* By invitation.

Florence C. H. Chu, M.D., John C. Lucas, Jr., M.D., and Joseph H. Farrow, M.D., Memorial Hospital, New York, New York.

0:55 A.M.

Physical and Clinical Parameters in the Management of Advanced Breast Cancer with Irradiation Alone. Eleanor D. Montague, M.D.,*
M. D. Anderson Hospital, Houston, Texas.

II: IO A.M.

St. Agatha and Inadequate Simple Mastectomy. Arthur J. Holleb, M.D., and Joseph H. Farrow, M.D., Memorial Hospital, New York, New York.

11:25 A.M.

An Attempt to Estimate the Value of Irradiation of the Regional Glands in the Treatment of Carcinoma of the Breast by Mastectomy and Irradiation. Margaret D. Snelling, M.D., F.R.C.S.,* Meyerstein Institute of Radiotherapy, Middlesex Hospital, London, England. President, British Institute of Radiology.

II:45 A.M.

Treatment of Osteogenic Sarcoma of the Mandible. Carl W. Boyer, Jr., M.D.,* and Gary P. Wratten, M.D.,* Adelphi and Silver Spring, Maryland.

12:00 NOON

The Diagnosis and Treatment of Metastatic Brain Disease with Antifibrin Antibody I¹³¹. Irving Spar, Ph.D.,* Philip Rubin, M.D., Jerold P. Green, M.D.,* and William Bale, Ph.D.,* University of Rochester School of Medicine and Dentistry, Rochester, New York.

12:15 P.M.

Malignant Lesions of the Nasopharynx: 142 Cases
Treated in an 11 Year Period, 1950-1960. Paul
W. Scanlon, M.D., R. E. Rhodes, M.D.,* L. B.
Woolner, M.D.,* K. D. Devine, M.D.,* and
J. B. McBean, M.D.,* Mayo Clinic, Rochester,
Minnesota.

12:30 P.M.

Treatment of Osteogenic and Soft Tissue Sarcomas. Adolph Zuppinger, M.D.,* University of Bern, Bern, Switzerland.

I:00 P.M.

Adjournment of First Scientific Session.

Thursday, April 14, 1966

8:∞ A.M.—4:∞ P.M.

Registration.

8:15 A.M.

First Executive Session—for All Members.

* By invitation.

SECOND SCIENTIFIC SESSION

Richard H. Jesse, M.D., Chairman.

M. D. Anderson Hospital, Houston, Texas.

9:00 A.M.

Pleural Mesothelioma: An Evaluation of 44 Cases. Erick R. Ratzer, M.D.,* Myron Melamed, M.D.,* and John L. Pool, M.D., Memorial Hospital, New York, New York.

9:15 A.M.

The Value of 2 MV. X-ray Therapy in Differentiated Thyroid Carcinoma. Magnus I. Smedal, M.D., Ferdinand A. Salzman, M.D.,* and William Meisser, M.D.,* Lahey Clinic, Boston, Massachusetts.

9:30 A.M.

Intra-arterial 5-Bromodeoxyuridine and X-ray Therapy. Malcolm A. Bagshaw, M.D., R. L. Scotte Doggett, M.D.,* Kendric C. Smith, Ph.D.,* Henry S. Kaplan, M.D., and Thomas S. Nelsen, M.D.,* Stanford University School of Medicine, Palo Alto, California.

9:45 A.M.

Treatment of Bone Metastases with Parathormone followed by Radiophosphorus. Eddy Chi-Kwang, M.D.,* and Sidney Rubenfeld, M.D., Bellevue Hospital, New York, New York.

 $10:\infty$ A.M.

Radiation Induced Hepatic Damage: Its Demonstration by Radioisotope Scanning. P. M. Johnson, M.D.,* F. M. Grossman, M. D.,* and H. L. Atkins, M.D.,* New York, New York.

10:15 A.M.

The Value of Strontium 85 Scanning in X-Ray Therapy. David M. Sklaroff, M.D., and N. David Charkes, M.D.,* Albert Einstein Medical Center, Philadelphia, Pennsylvania.

10:30 A.M.

Color Scanning of Bone for the Diagnosis of Cancer. Henry L. Jaffe, M.D., Cedars of Lebanon Hospital, Los Angeles, California.

10:45 A.M.

The Gamma Camera: A Widening of Scanning Horizons. Joseph E. Stapleton, M.D., James F. Clifton, B.A.,* and Michael R. McKamey, B.Sc.,* Tumor Institute, Swedish Hospital, Seattle, Washington.

II: ∞ A.M.

Hodgkin's Disease: Iso-effect Tumor Lethal Dose Studies. Milton Friedman, M.D., Alexander Pearlman, M.D.,* and Max A. Woodbury, Ph.D.,* University Hospital, New York, New York.

11:15 A.M.

Cancer Therapy: Present Status and Future Trends. R. Lee Clark, Jr., M.D.,* M. D. Anderson Hospital, Houston, Texas.

11:35 A.M.

Symposium: The Advantages and Disadvantages of Electron Beam Therapy.

Charles Botstein, M.D., Chairman.

Montefiore Hospital, New York, New York.

Participants:

Adolph Zuppinger, M.D.,* University of Bern, Bern, Switzerland.

Maurice Tubiana, M.D.,* Institut Gustav Roussy, Villejuif, Seine, France.

John S. Laughlin, Ph.D., Memorial Hospital, New York, New York.

Melvin L. Griem, M.D., University of Chicago, Chicago, Illirois.

Norah DuV. Tapley, M.D., M. D. Anderson Hospital, Hcuston, Texas.

Gilbert H. Fletcher, M.D., M. D. Anderson Hospital, Hcuston, Texas.

I:00 P.M.

Adjournment of Second Scientific Session.

Friday, April 15, 1966

8:∞ A.M.—4:∞ P.N.

Registration.

8:15 A.M.

Second Executive Session—for All Members.

THIRD SCIENTIFIC SESSION

Juan A. del Regato, M.D., Chairman. Penrose Canzer Hospital, Colorado Springs, Colorado.

9:00 A.M.

Treatment of Primary Adenocarcinoma of the Cervix. Carlo A. Cuccia, M.D., Fernando G. Bloedorn, M.D., and Mustafa Onal, M.D.,* University of Maryland Hospital, Baltimore, Maryland.

9:15 A.M.

Carcinoma of the Floor of the Mouth. José N. Correa, M.D.,* Antonio Bosch, M.D.,* and Victor A. Marcial, M.D., Puerto Rico Nuclear Center, Puerto Rico.

9:30 A.M.

A Direct Reading Intracavitary Dosimeter for Use in Radium Therapy. Norman A. Baily, Ph.D.,* and Amos Norman, Ph.D.,* University of Californ a Center for the Health Sciences, Los Angeles, California.

9:45 A.M.

The Use of Radiation Therapy in the Treatment of Ophthalmclogic Lesions. M. Lederman, M.B., Royal Marsden Hospital, London, England.

10:05 A.M.

The Value of Liver Scans in the Management of Patients with Malignant Lymphoma. David W. Molander, M.D., Pack Medical Foundation, New York, New York.

^{*} By invitation.

^{*} By invitation.

10:20 A.M.

The Search For Hidden Cancer. Leo G. Rigler, M.D.,* University of California Center for the Health Sciences, Los Angeles, California.

IQ:40 A.M.

Cobalt 60 Teletherapy of Early Carcinomas of the Vocal Cords. C. M. Chahbazian, M.D., and J. A. del Regato, M.D., Penrose Cancer Hospital, Colorado Springs, Colorado.

10:55 A.M.

Hyperbaric Radiation Therapy: A Review of 2 Years' Experience. Henry P. Plenk, M.D., and Richard Y. Card, M.D.,* St. Mark's Hospital, Salt Lake City, Utah.

II: IO A.M.

Residual Radiopaque Bolus in Managing Intraspinal Neoplasms. Charles Martin, M.D.,* Eugene Gedgaudas, M.D.,* and G. J. D'Angio, M.D., University of Minnesota Hospital, Minneapolis, Minnesota.

II:25 A.M.

Radiation and the Epidemiology of Cancer—Etiologic and Therapeutic Aspects. Lester Breslow, M.D.,* Chief, Division of Preventive Medical Services, Department of Public Health, Berkeley, California.

II:45 A.M.

High Pressure Oxygenation and Dose Fractionation in Animal Tumors. Herman Suit, M.D.,*
M. D. Anderson Hospital, Houston, Texas.

12:05 P.M.

The History of the American Radium Society. Edith H. Quimby, Sc.D., Columbia University, New York, New York.

12:25 P.M.

THE JANEWAY LECTURE

The Problem of the Local Recurrence of Malignant Melanoma. Gordon P. McNeer, M.D. New York, New York.

1:15 P.M.

Adjournment of the Third Scientific Session.

6:15 P.M

Reception for All Members and Guests. Host: Radium Chemical Company.

7:30 P.M.

Annual Banquet. Presentation of Janeway Medal. Entertainment.

Saturday, April 16, 1966

8:15 A.M.

Third Executive Session—for All Members.

FOURTH SCIENTIFIC SESSION
John L. Pool, M.D., Chairman.
Memorial Hospital, New York.

* By invitation.

9:00 A.M.

The Synergistic Effect of Laser Radiation and Ionizing Radiation of Malignant Tumors In Vivo and In Vitro. James T. Helsper, M.D., George S. Sharp, M.D., and Donald E. Rounds, Ph.D.,* Pasadena, California.

9:15 A.M.

The Place of Radiotherapy in Treatment of Malignant Metastatic Glands of the Neck. Vera M. Dalley, M.D.,* The Royal Marsden Hospital, London, England.

9:30 A.M

The Use of Radiographic Methods in the Classification in Staging of Laryngeal Tumors. T. R. Howell, M.D.,* M. May, M.D.,* G. A. Gildersleeve, M.D.,* and E. Richard King, M.D., Medical College of Virginia, Richmond, Virginia.

9:45 A.M.

Transvaginal Cesium Therapy. Jerome M. Vaeth, M.D., Mount Zion Hospital, San Francisco, California.

10:00 A.M.

Studies of the Action of Chemotherapeutic Agents at the Cellular Level. W. R. Bruce, M.D.,* The Ontario Cancer Institute, Toronto, Canada.

10:15 A.M.

Twenty-five Years' Experience with Supervoltage Therapy in the Treatment of Bladder Cancer. Franz J. Buschke, M.D., and George Jack, M.D.,* University of California Medical Center, San Francisco, California.

10:30 A.M.

Pineal Body Tumors. John G. Maier, Lt. Col., M.C., USA.,* and David DeJong, Major, M.C., USA.,* Walter Reed General Hospital, Washington, D.C.

10:45 A.M.

Management of Malignant Lymphomas and Hodgkin's Disease Limited to the Head and Neck. Lillian M. Fuller, M.D., M. D. Anderson Hospital, Houston, Texas.

11:00 A.M.

Cobalt 60 Telecurietherapy, with and without Surgery in the Definitive Treatment of Cancer of the Testicle. Frederick W. George, III, Capt., MC, USN., Robert F. Dykhiuzen, M.D.,* and Samuel S. Kirrohara, M.D.,* U. S. Naval Hospital, San Diego, California.

11:15 A.M.

The Effects of Irradiation (External and Internal) on the Lymphatic Dynamics. Irving M. Ariel, M.D., and Michael J. Resnick, M.D.,* Pack Foundation, New York, New York.

11:30 а.м.

Preservation of the Larynx in the Surgical Treat-

^{*} By invitation.

ment of Cancer, Recurrent after Radiation Therapy. A. J. Ballantyne, M.D., and Gilbert H. Fletcher, M.D., M. D. Anderson Hospital, Houston, Texas.

11:45 A.M.

The Application of Newer Radiobiology Knowledge to Radiation Therapy. Maurice Tubiana, M.D.,* Institut Gustav Roussy, Villejuif, Seine, France.

* By invitation.

12:15 P.M.

The Surgical Treatment of Carcinoma of the Cervix after Radiation Therapy. Alexander Brunschwig, M.D., Memorial Hospital, New York, New York.

12:35 P.M.

Final Executive Session for All Members and Installation of New Officers. Adjournment of the Forty-eighth Annual Meeting of the American Radium Society.



NEWS ITEMS

INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION

The following are the officers and members of the International Commission on Radiological Protection for the period 1965–1969: Dr. E. E. Pochin, Chairman (Great Britain); Dr. C. G. Stewart, Vice-Chairman (Canada); Professor L. Bugnard (France); Professor O. Hug (Germany); Dr. H. Jammet (France); Professor A. A. Letavet (U.S.S.R.); Professor B. Lindell (Sweden); Dr. J. F. Loutit (Great Britain); Dr. H. Z. Morgan (U.S.A.); Dr. H. B. Newcombe (Canada); Dr. C. C. Powell (U.S.A.); Dr. L. S. Taylor (U.S.A.); and Professor B. Windeyer (Great Britain).

Professor R. M. Sievert of Sweden is Chairman Emeritus and Dr. F. D. Sowby of Canada is Scientific Secretary.

The Commission's secretariat is at Clifton Avenue, Sutton, Surrey, England.

COURSE IN CLINICAL USE OF RADIOACTIVE ISOTOPES

A course in the "Clinical Use of Radioactive Isotopes" will be given under the supervision of Dr. Sergei Feitelberg, Dr. Solomon Silver and Dr. Edith Quimby of the Department of Radiology, Columbia University, New York City, from June 6 through July 1, 1966.

This is a full-time course which includes lectures, experimental laboratory exercises, clinical rounds and clinical measurements on patients and on specimens.

In addition to Drs. Feitelberg, Silver and Quimby, the teaching staff will include a number of invited lecturers from the New York area, each presenting material in his own special field.

Enrollment in the class is limited to 20. Inquires should be addressed to Dr. Sergei Feitelberg, Mt. Sinai Hospital, Fifth Avenue at 100th Street, New York, New York.

INTERNATIONAL RADIATION PROTEC-TION ASSOCIATION (IRPA)

The First International Congress of the International Radiation Protection Association (IRPA) will convene in Rome, Italy, September ς -10, 1966.

For further information regarding the Congress, contact: Dr. C. Polvani, Secretary General, First International Congress of the International Radiation Protection Association, Casella Postale 2359, Roma, Italy.

NINTH INTERNATIONAL CANCER CONGRESS

In connection with the Ninth International Cancer Congress, which will take place in Tokyo, Japan, October 23–29, 1966, a charter flight and several group flights are contemplated, thus substantially reducing the cost of transportation. Members of the immediate family of congress participants will be eligible.

Anyone interested should communicate with Hirsch Marks, M.D., 435 East 57th Street, New York 22, New York.

POSTGRADUATE SYMPOSIUM

The University of Kansas School of Medicine will present its Nineteenth Annual Postgraduate Symposium on "Radiology and Radioactive Isotopes" on February 14–16, 1966.

The guest faculty includes: Charles C. Burkell, M.D., University of Saskatchewan; Harry W. Fischer, M.D., State University of Iowa; Robert D. Moseley, Jr., M.D., University of Chicago; Sidney W. Nelson, M.D., Ohio State University; Klaus Ranniger, M.D., University of Chicago; Harvey White, M.D., Northwestern University; and Jerome F. Wiot, M.D., University of Cincinnati.

For program announcement and information, write Department of Postgraduate Medical Education, University of Kansas School of Medicine, 39th and Rainbow Blvd., Kansas City, Kansas 66103.

BOOK REVIEW

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Vascular Roentgenology: Arteriography, Phlebography, Lymphography. Edited by Robert A. Schobinger, M.D., F.A.C.A., F.I.C.A., S.G.P., Diplomate, American Board of Surgery; Diplomate F.M.H. in Surgery, Switzerland; Department of Surgery, Clinic St. Anna, Lucerne, Switzerland; and Francis F. Ruzicka, Jr., M.D., F.A.C.R., Director, Department of Radiology, The St. Vincent's Hospital and Medical Center, New York; Clinical Professor of Radiology, New York University School of Medicine, New York. Cloth. Pp. 747, with many illustrations. The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1964.

This book, which contains the experiences of 93 contributors, covers the whole field of vascular roentgenology and lymphography. It is conveniently divided into 5 parts beginning with General Considerations of Angiography followed by Angiocardiography, Arteriography, Phlebography and Lymphography. The subject matter is presented with commendable clarity in all sections, using adequate quotation of pertinent references. The numerous illustrations are excellent and are easily recognizable as examples of the condition under discussion, a factor which is a frequent source of frustration in the reproduction of roentgenograms in many textbooks.

Since the reviewer cannot claim to be more than superficially acquainted with many of the procedures described, comment will be confined to Part I—General Considerations and Part III—Arteriography with particular reference to cerebral arteriography in the latter section.

Part I begins with a brief review of the history of angiography and continues with a discussion of materials used, the pharmacology of the contrast media, and the general principles of anesthesia. This is followed by a description of certain techniques in general use such as the vascular cut down, percutaneous selective angiography and cineangiography. The section on equipment necessarily reflects the personal choice of the authors in the use of needles, catheters, and pressure injectors. There is also

a tendency to emphasize direct vertebral angiography, a procedure which has nothing to commend it.

Part III contains 15 sections each covering a different aspect of arteriography. The basic approach is the same in all cases with a brief but adequate anatomic description followed by a technique, results and complications.

In the section covering angiography of the head and neck, nearly all possible methods of angiography are described with no apparent attempt to differentiate between those that are obsolete and those recommended for use, although angiography has now developed to the extent that certain techniques are obsolete and, in addition, carry a higher rate of complications. This is particularly true of vertebral arteriography by direct puncture which does not deserve the prominence given in this section. One would like to see more emphasis on methods which give maximum information at the least risk to the patient.

This is a valuable reference book for those engaged in one or more of the so many types of vascular roentgenology and for those whose work brings them into contact with angiography.

John Gilroy, M.D.

BOOKS RECEIVED

GAZZETTA INTERNAZIONALE DE MEDICINA E CHIRURGIA. December, 1964, Volume, 69. Direttore Responsabile: Prof. Carlo Bazzicalupo. Paper. Pp. 999, with many illustrations. Edizioni Mediche e Scientifiche, Largo A. Ravizza, 17, Rome, Italy, 1964.

PRAKTISCHE GASTROENTEROLOGIE. By Dr. Ernst Hafter, Beratender Gastroenterologe der Medizinischen Universitätsklinik mit Lehrauftrag für Gastroenterologie an der Medizinischen Fakultät Zürich. Cloth. Pp. 554, with 195 illustrations. Price, Ganzleinen DM 64,—. Georg Thieme Verlag, Postfach 732, Herdweg 63, 7000 Stuttgart 1, Germany, 1965.

Beckenosteotomie Pfannendachplastik. Internationales Symposium, January 30, 31, 1965, Basel. Edited by Prof. Dr. G. Chapchal, Vorsteher der Orthopädischen Universitätsklinik Basel. Paper. Pp. 131, with 79 illustrations. Price,

DM 35,—. Georg Thieme Verlag, Postfach 732, Herdweg 63, 7000 Stuttgart I, Germany, 1965.

Dosimetrie zur Betatrontherapie. By Priv.-Doz. Dr. Wolfgang Pohlit, Max-Planck-Institut für Biophysik, Frankfurt am Main. Paper. Pp. 80, with 55 illustrations. Price, DM 24,—. Georg Thieme Verlag, Postfach 732, Herdweg 63, 7000 Stuttgart 1, Germany, 1965.

RÖNTGENOLOGISCHE HERZVOLUMENBESTIMMUNG IN KLINIK UND PRAXIS. By Prof. Dr. Helmut Klepzig, and Dr. Peter Frisch, Klinik der Krankenversorgung der Bundesbahnbeamten für Herzund Gefässkrankheiten, Königstein i. Ts. Paper. Pp. 56, with 26 figures. Price, DM 18,—. Georg Thieme Verlag, Postfach 732, Herdweg 63, 7000 Stuttgart I, Germany, 1965.

RADIOGRAPHIC PHOTOGRAPHY. By D. Noreen Chesney, Hon. F.S.R. T.E. S.R.R., Superintendent Teacher, School of Radiography, Coventry and Warwickshire Hospital; and Muriel O. Chesney, F.S.R. T.E. S.R.R., Teacher Principal, School of Radiography, The United Birmingham Hospitals. Cloth. Pp. 447, with 113 illustrations. Price, \$10.00. F. A. Davis Co., 1914 Cherry Street, Philadelphia, Pa., 1965.

THE CHEST FILM IN MASSIVE PULMONARY EMBOLISM. By Daniel J. Torrance, Jr., M.D., Member, Scripps Clinic and Research Foundation; Chief, Division of Diagnostic Roentgenology, La Jolla Calif.; Formerly, Associate Professor, The Johns Hopkins University School of Medicine; and Chief, Division of Diagnostic Roentgenology, The Johns Hopkins Hospital and Medical School, Baltimore, Md. Cloth. Pp. 74, with 31 il-

lustrations. Price, \$6.75. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1963.

DIAGNOSTIC RADIOLOGIC INSTRUMENTATION: MOD-ULATION TRANSFER FUNCTION. Edited by Robert D. Moseley, Jr., M.D., Professor of Radiology; Chairman, Department of Radiology, The University of Chicago, Chicago, Ill.; and John H. Rust, D.V.M., Ph.D., Professor of Pharmacology; Head Section of Nuclear Medicine, Department of Pharmacology, The University of Chicago, Chicago, Ill. Cloth. Pp. 423, with many illustrations. Price, \$17.50. Charles C Thomas, Publisher, 301– 327 East Lawrence Avenue, Springfield, Ill., 1965.

THE INFLUENCE OF HORMONAL TREATMENT AND ORCHIECTOMY, OOPHORECTOMY AND THYROIDECTOMY ON EXPERIMENTAL FRACTURES. A Quantitative P**-Auoradiographic, Roentgenologic and Tissue-analytic Study. By Erkki V. S. Koskinen. Paper. Pp. 40, with some illustrations. Acta Orthopaedica Scandinavica, Supplementum No. 80. Munksgaard, Copenhagen, 1965.

THE DEVELOPMENT OF SPINAL DEFORMITY IN EX-PERIMENTAL SCOLIOSIS. By Jarl-Erik Michelsson. Paper. Pp. 91, with many illustrations. Acta Orthopaedica Scandinavica, Supplementum No. 81. Munksgaard, Copenhagen, 1965.

Transplantation of Epiphyseal Cartilage and Cranial Suture. Experimental Studies on the Preservation of the Growth Capacity in Growing Bone Grafts. By Soini Ryöppy. Paper. Pp. 107, with many illustrations. Acta Orthopaedica Scandinavica, Supplementum No. 82. Munksgaard, Copenhagen, 1965.



SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society

Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: San Francisco Hilton Hotel, San Francisco, Calif., Sept. 27–30, 1966. American Radium Society

Secretary, Dr. John L. Pool, 444 East 68th Street, New York, N. Y. 10021. Annual meeting: Camelback Inn, Phoenix, Ariz., April 13-16, 1966 (Golden Anniversary).

RADIOLOGICAL SOCIETY OF NORTH AMERICA

Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting to be announced.

AMERICAN COLLEGE OF RADIOLOGY

AMERICAN COLLEGE OF RADIOLOGY

Executive Director, William C. Stronach, 20 N. Wacker
Drive, Chicago 6, Ill. Annual meeting: Drake Hotel,
Chicago, Ill., Feb. 1-5, 1966.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eighth Ave., Spokane 4, Wash. Annual
meeting: Chicago, Ill., June 26-30, 1966.

AMERICAN BOARD OF RADIOLOGY

American Board of Radiology

Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn. The Spring 1966 examination will be held at the Ter-race Hilton Hotel, Cincinnati, Ohio, June 6-10, inclusive. The deadline for filing applications for this examination

was December 31, 1965.

The Fall 1966 examination will be held at the Washington Hilton Hotel, Washington, D.C., December 5-9, inclusive. The deadline for filing applications is June 30,

1966.

American Association of Physicists in Medicine Secretary, Leonard Stanton, Hahnemann Medical College, 230 N. Broad St., Philadelphia, Pa. 19102. Annual meeting to be announced.

AMERICAN CLUB OF THERAPEUTIC RADIOLOGISTS Secretary, Dr. J. A. del Regato, Penrose Cancer Hospital,

Colorado Springs, Colo.

ELEVENTH INTERNATIONAL CONGRESS OF RADIOLOGY Secretary-General, Professor Dr. Med. Arduino Ratti, via Moscova, 44-1, Milan, Italy. Address inquiries to Professor Dr. Med. Luigi Turano, President-Elect, Istituto di Radiologia, Università di Roma, Rome, Italy. Ninth Inter-American Congress of Radiology

Counselor for the United States, Dr. Philip J. Hodes, Jefferson Medical College Hospital, 11th and Walnut Streets, Philadelphia 7, Pennsylvania. President, Dr. Leandro Zubiaurre, Montevideo, Uruguay.

Meeting: Montevideo, Uruguay, 1967. Inter-American College of Radiology

President, Dr. Oscar Soto, H. Urteaga 480, Lima, Perú.

ALABAMA RADIOLOGICAL SOCIETY

Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place of Alabama State Medical Association. American Ñuclear Society

Treasurer, Raymond Maxson, 86 E. Randolph St., Chicago, Ill. Annual meeting to be announced.

Arizona Radiological Society

Secretary-Treasurer, Dr. George Gentner, 3435 W. Durango, Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Chapter of American College of Radiology

Secretary-Treasurer, Dr. James R. Mcrrison, 550 S. University, Little Rock, Ark. 72205.
Arkansas Radiological Society

Secretary, Dr. Charles W. Anderson, 11081 Poplar. Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists

Secretary-Treasurer, Dr. Morton M. Kligerman, Dept. of Radiology, Yale University Medica School, New Haven, Conn. Annual meeting: University of Arkansas, Little Rock, Ark., May 13-14, 1966.

ATLANTA RADIOLOGICAL SOCIETY

Secretary, Dr. Donald R. Rooney, Burnt Hickory Road, Marietta, Ga. Meets monthly except during three summer months, on third Tuesday, at the Acedemy of Medi-

cine, Atlanta, Ga., at 8:00 P.M. BAVARIAN-AMERICAN RADIOLOGIC SOCIETY

Secretary, Dr. Roy R. Deffebach, Major, MC, Radiology Service, 5th General Hospital, APO 154, New York, N. Y. Meets quarterly.

BLOCKLEY RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. R. John Gould, 441 Lombardy Rd., Drexel Hill, Pa. 19026.

BLUEGRASS RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Arthur Lieber, University of Kentucky, University Hospital, Lexington, Kentucky. Meets quarterly.

Brooklyn Radiological Society

Secretary, Dr. Edward Feely, St. Johns Episcopal Hospital, 480 Herkimer St., Brooklyn, N. Y. Meets first Thursday of each month, October through June.

BUFFALO RADIOLOGICAL SOCIETY

Secretary, Dr. Richard Munschauer, 130 Hodge Ave., Buffalo, N.Y. 14222. Meets second Monday evening each month, October to May inclusive.

CALIFORNIA RADIOLOGICAL SOCIETY

Secretary, Dr. L. Henry Garland, Suite 1739, 450 Sutter St., San Francisco, Calif. Meets annually during meeting of California Medical Association.

CATAWBA VALLEY RADIOLOGICAL SOCIETY

Secretary, Dr. Emmett R. White, P. O. Box 303, Rutherford College, N. C. Meets every Tuesday, Dept. of Radiology, Valdese General Hosp., Valdese, N. C. at

CENTRAL NEW YORK RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Edward W. Carsky, Crouse-Irving Hospital, 820 S. Crouse Ave., S-racuse, N. Y. Meets first Monday each month, October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Atis K. Freimanis, Ohio State Univ. Hospitals, 410 W. 10th Ave., Columbus, Ohio 43210. Meets second Thursday in October, November, January, and March 15 and May 19 at Fort Hayes Hotel, Columbus, Ohio.

CENTRAL SOCIETY OF NUCLEAR MEDICINE
Secretary, Dr. Robert S. Landauer, Radiation Center Bldg., 1903 West Harrison St., Chicago 12, Ill.

CHICAGO ROENTGEN SOCIETY

Secretary-Treasurer, Dr. Robert D. Moseley, Jr., Dept. of Radiology, Univ. of Chicago, 950 E. 59th St., Chicago 37, Ill. Meets second Thursday of each month, October to April except December at the Pick-Congress Hotel at

CLEVELAND RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. James Christie, 10515 Carnegie

Secretaries of societies are requested to send timely information promptly to the Editor.

Avenue, Cleveland, Ohio. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.

COLORADO RADIOLOGICAL SOCIETY

Secretary, Dr. George F. Wertz, 1801 High St., Denver, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

CONNECTICUT VALLEY RADIOLOGIC SOCIETY

Secretary, Dr. William W. Walthall, Jr., 130 Maple St., Springfield, Mass. Meets in April and October.

DALLAS-FORT WORTH RADIOLOGICAL SOCIETY

Secretary, Dr. R. E. Collier, 3500 Gaston Ave., Dallas,
Tex. Meets monthly, third Monday, at Southwest Inter-

national Airport at 6:30 г.м.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY Secretary, Dr. Robert L. Willis, Harper Hospital, Detroit I, Mich. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30

EAST BAY ROENTGEN SOCIETY

Secretary, Dr. William G. Faraghan, 450 30th St., Oakland 9, Calif. Meets first Thursday each month at University Club, Oakland, Calif.

EAST TENNESSEE RADIOLOGICAL SOCIETY

Secretary, Dr. C. H. Kimball, 2200 Harris Circle, Cleveland, Tenn. Meets in January and September.

EASTERN RADIOLOGICAL SOCIETY

Secretary, Dr. James F. Martin, North Carolina Baptist
Hospital, Winston-Salem, N. C.

FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. John C. Jowett, Orlando, Fla. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Garth R. Drewry, Tampa General Hospital, Tampa 6, Fla. Meets in January, April, July and October.

Georgia Radiological Society

Secretary, Dr. I. R. Berger, 1010 Prince Ave., Athens, Ga. Meets in spring and fall with Annual State Society

Meeting.

Greater Miami Radiological Society Secretary-Treasurer, Dr. Oliver P. Winslow, Jr., Baptist Hospital of Miami, Inc., 8900 S. W. 88th St., Miami 56, Fla. Meets monthly, third Wednesday at 8:00 P.M. at Jackson Memorial Hospital, Miami, Fla.

GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS

Secretary-Treasurer, Dr. Mark D. Eagleton, 950 Francis Place, St. Louis, Mo

HOUSTON RADIOLOGICAL SOCIETY

Secretary, Dr. D. A. Van Velzer, Texas Medical Center Library, Jesse H. Jones Library Bldg., Houston 25, Tex. Meets fourth Monday of each month, except June, July, August and December, at the Doctors' Club, 8:∞ P.M., Houston, Tex.

IDAHO STATE RADIOLOGICAL SOCIETY

Secretary, Dr. George H. Harris, Bannock Memorial Hcspital, Pocatello, Idaho. Meets in the spring and fall.

Illinois Radiological Society

Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

Indiana Roentgen Society, Inc.

Secretary, Dr. Richard A. Silver, 1815 N. Capitol Avenue, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

IOWA RADIOLOGICAL SOCIETY

Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Robert C. Lawson, 310 Medical Arts Bldg., 10th and Home, Topeka, Kan. Meets in spring with State Medical Society and in winter on call.

KENTUCKY CHAPTER, AMERICAN COLLEGE OF RADIOLOGY Secretary-Treasurer, Dr. Robert H. Greenlaw, Dept. of Radiology, Univ. of Kentucky Med. Ctr., Lexington, Ky. Meets semiannually.

KENTUCKY RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Joan R. Hale, 402 Heyburn Building, Louisville, Ky. Meets monthly on second Friday at Sheraton Hotel, Louisville, Ky.

KINGS COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

KNOXVILLE RADIOLOGICAL SOCIETY

Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

LONG ISLAND RADIOLOGICAL SOCIETY

Secretary, Dr. David Faegenburg, Nassau Academy of Medicine, 1200 Stewart Ave., Garden City, L. I., N. Y. 11533. Meets second Tuesday of the month in February, April, June, October and December.

Los Angeles Radiological Society

Secretary, Dr. Joseph A. Parks, 15107 Vanowen St., Van Nuys, Calif. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los

LOUISIANA-TEXAS GULF COAST RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Edward A. Sheldon, 109 Doctors Bldg., Beaumont, Texas 77701.

MAINE RADIOLOGICAL SOCIETY

Secretary, Dr. J. T. Chen, 7 Cherry Hill Terrace, Water-ville, Me. Meets in June, September, December and April.

MARYLAND RADIOLOGICAL SOCIETY

Secretary, Dr. Henry Startzman, Medical Arts Building, Baltimore, Md.

MEMPHIS ROENTGEN SOCIETY

Secretary-Treasurer, Dr. Vernon I. Smith, Jr., Suite 203, 1085 Madison Ave., Memphis, Tenn. 38104. Meets first Monday of each month at John Gaston Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY

Secretary, Dr. William D. Roberts, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

MID-HUDSON RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Alexander W. Friedman, Mid-Hudson Medical Group, Fishkill, N. Y. Meets 7:00 P.M., first Wednesday of each month September to May.

MILWAUKEE ROENTGEN RAY SOCIETY

Secretary-Treasurer, Dr. Donald P. Babbitt, 1700 W. Wisconsin Ave., Milwaukee, Wis. 53233. Meets monthly on fourth Monday, October through May, at University Club.

MINNESOTA RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Edward A. Peterson, St. Paul, Minn. Meets twice annually, fall and winter.

MISSISSIPPI RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Dan T. Keel, Jr., 504 Chippewa St., Brookhaven, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 p.m.

MISSOURI RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. M. Shoss, Cape Girardeau, Mo.

MONTANA RADIOLOGICAL SOCIETY

Secretary, Dr. Clark Grimm, Great Falls, Montana. Meets at least once a year.

NEBRASKA STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Richard Bunting, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEVADA RADIOLOGICAL SOCIETY

Secretary, Dr. William G. Arbonies, Department of Radiology, St. Mary's Hospital, Reno, Nev.

NEW ENGLAND ROENTGEN RAY SOCIETY

Secretary, Dr. Jack R. Dreyfuss, Zero Emerson Place, Boston, Mass. 02114. Meets third Friday of each month, October through April, at The Longwood Towers, 20 Chapel Street, Brookline, Mass., at 4:30 P.M.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

New Mexico Association of Radiologists

Secretary-Treasurer, Dr. Justin J. Wolfson, Department of Radiology, Bernalillo County-Indian Hospital, Albuquerque, New Mexico.

NEW MEXICO SOCIETY OF RADIOLOGISTS

Secretary, Dr. William G. McPheron, Hobbs, New Mexico. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

New York Roentgen Society Secretary, Dr. Milton Elkin, Albert Einstein College of Medicine, Bronx, N.Y. 10461. Meets monthly on third Monday at the New York Academy of Medicine at 4:30

NORTH CAROLINA RADIOLOGICAL SOCIETY Secretary, Dr. E. H. Schultz, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in the spring and fall each year.

NORTH DAKOTA RADIOLOGICAL SOCIETY

Secretary, Dr. Robert J. Olson, 1240 8th Ave., Williston, N. D. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

NORTH FLORIDA RADIOLOGICAL SOCIETY Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY Secretary, Dr. Anthony J. Tabacco, 621 Central Ave., Albany 6, N. Y. Meets in Albany area on second Wednes-day of October, November, March and April.

NORTHERN CALIFORNIA RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. John Turner, 1215-28th St., Sacramento, Calif. Meets fourth Monday of Sept., Nov., Jan., March and May at the Sutter Club in Sacramento.
Northwestern Ohio Radiological Society

Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department of Radiology, Toledo, Ohio.
Ohio State Radiological Society

Secretary, Dr. Mortimer Lubert, Cleveland, Ohio. Annual meeting: Toledo, Ohio, May 13-15, 1966.

OKLAHOMA STATE RADIOLOGICAL SOCIETY Secretary, Dr. Robert Sukman, 1200 N. Walker, Okla-

homa City, Okla. Meets in January, May and October. ORANGE COUNTY RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Herbert H. Benson, 100 East

Valencia-Mesa Dr., Fullerton, Calif. Meets fourth Tuesday of every month in Orange County Medical Association Building. OREGON RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Robert S. Miller, 13753 S.W.

Farmington Rd., Beaverton, Ore. 97005. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

ORLEANS PARISH RADIOLOGICAL SOCIETY

Secretary, Dr. Joseph V. Schlosser, Charity Hospital,
New Orleans 13, La. Meets second Tuesday of each month. PACIFIC NORTHWEST RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Willis Taylor, 1118 9th Ave., Seattle, Washington. Annual meeting to be announced. Pennsylvania Radiological Society

Secretary, Dr. T. Frederick Weiland, Jr., 619 Ridgeway Ave., Grove City, Pa. Annual meeting: Hotel Hershey,

May 12-14, 1966.
PHILADELPHIA ROBITGEN RAY SOCIETY

Secretary, Dr. C. Jules Rominger, Misericordia Hospital, 54th St. and Cedar Ave., Philadelphia, Pa. 19143. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY Secretary, Dr. Robert N. Berk, 3305 Fifth Ave., Pittsburgh 13, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

RADIOLOGICAL SOCIETY OF CONNECTICUT, INC.

Secretary-Treasurer, Dr. Orlando F. Gabriele, 1450
Chapel St., New Haven 11, Conn. Meetings are held quarterly.

RADIOLOGICAL SOCIETY OF GREATER CINCINNATI Secretary, Dr. Harold N. Margolin, 6159 Tulane Road, Cincinnati, Ohio. Meets first Monday of each month at Cincinnati Academy of Medicine.

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

RADIOLOGICAL SOCIETY OF HAWAII

Secretary-Treasurer, Dr. Robert W. Edland, P.O. Box 282, USA Tripler General Hospital, Honolulu, Hawaii. Meets third Monday of each month at 7:30 P.M.

RADIOLOGICAL SOCIETY OF KANSAS CITY

Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas
City, Mo. Meets third Thursday of each month.

RADIOLOGICAL SOCIETY OF LOUISIANA

Secretary, Dr. Lester W. Eavenson, 2700 Napoleon Ave., New Orleans 15, La. Meets semiannually, during Louisiana State Medical Society meeting and 6 months later. RADIOLOGICAL SOCIETY OF NEW JERSEY

Secretary, Dr. E. Arthur Kratzman, 912 Prospect Ave., Plainfield, N. J. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

RADIOLOGICAL SOCIETY OF RHODE ISLAND Secretary-Treasurer, Dr. John M. Vesey, 1196 Elmwood Ave., Cranston, R. I.

RADIOLOGICAL SOCIETY OF SOUTH DAKOTA Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

RADIOLOGICAL SOCIETY OF SOUTHERN CALIFORNIA Secretary-Treasurer, Dr. Gerald M. McDonnel, U.C.L.A. Medical Center for Health Sciences, Los Angeles, Calif. 90024. Meets three times a year, usually October, February, and May.

RADIOLOGICAL SOCIETY OF THE STATE OF NEW YORK Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y.

REDWOOD EMPIRE RADIOLOGICAL SOCIETY Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

RICHMOND COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. W. F. Hamilton, Jr., University Hospital,
Augusta, Ga. Meets first Thursday of each month at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y. Secretary, Dr. Irving B. Joffe, Rochester General Hospital, 1425 Portland Ave., Rochester 21, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY Secretary-Treasurer, Dr. Robert W. Lackey, 4200 E. Ninth Ave., Denver, Colo. Annual meeting: Brown Palace Hotel, Denver, Colo., Aug. 18-20, 1966.
SAN ANTONIO-MILITARY RADIOLOGICAL SOCIETY

Secretary, Dr. Hugho F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Tex. Meets third Wednesday of each month in Fort Sam Houston Officer's Club at 6:30 P.M.

SAN DIEGO RADIOLOGICAL SOCIETY

President-Secretary, Charles P. Hyslop, 7901 Frost St.,
San Diego 22, Calif. Meets first Wednesday of each
month at the University Club.

SAN FRANCISCO RADIOLOGICAL SOCIETY Secretary, Dr. Malcolm Jones, University of California Hospital, San Francisco 22, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

Section on Radiology, California Medical Association Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

SECTION ON RADIOLOGY, MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA Secretary-Treasurer, Dr. George T. Hennessey, Washington, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at

SECTION ON RADIOLOGY, SOUTHERN MEDICAL ASSOCIATION Secretary, Dr. Andrew F. Giesen, Jr., White-Wilson Clinic, Fort Walton Beach, Fla. Annual meeting:

Houston, Texas, Nov. 1-4, 1966.

Section on Radiology, Texas Medical Association

Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Médical Association.

SHREVEPORT RADIOLOGICAL CLUB

Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY

Secretary, Dr. John L. Gwinn, Children's Hospital, 4614 Sunset Blvd., Los Angeles 27, Calif. Annual meeting: San Francisco Hilton Hotel, San Francisco, Calif., Sept. 26, 1966.

Society of Nuclear Medicine
Secretary, Mr. C. Craig Harris, Oak Ridge National
Laboratories, Oak Ridge, Tenn. Administrator, Mr.
Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting to be announced.

SOUTH BAY RADIOLOGICAL SOCIETY

Secretary, Northern Section: Dr. John H. Callaghan, 2900 Whipple Ave., Redwood City, Calif.; Southern Section: Dr. Carleton J. Wright, 2015 Clarman Way, San Jose, Calif. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at

time and place designated by the president. South Dakota Radiological Society

Secretary, Dr. Donald J. Peik, 1417 S. Minnesota Ave., Sioux Falls, S. Dak. Meets in spring with State Medical Society and in fall.

Southern Radiological Conference Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala. Annual meeting: Grand Hotel, Point Clear, Ala., Jan. 28–30, 1966.

SOUTHWESTERN RADIOLOGICAL SOCIETY

Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

TENNESSEE RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. E. K. Carter, Holston Valley Community Hosp., Kingsport, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

TEXAS RADIOLOGICAL SOCIETY

Secretary, Dr. Herman C. Sehested, 815 Medical Arts Bldg., Fort Worth 2, Tex. Annual meeting: Driscoll Hotel, Corpus Christi, Jan. 28–29, 1966.

TRI-STATE RADIOLOGICAL SOCIETY

Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Cct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

University of Michigan Department of Roentgen-OLOGY STAFF MEETING

Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital, Ann Arbor, Mich.

UPPER PENINSULA RADIOLOGICAL SOCIETY Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

UTAH STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Carlisle C. Smith, Salt Lake General Hospital, 2033 S. State St., Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Vermont Radiological Society
Secretary, Dr. John R. Williams, 160 Allen St., Rutland,

VIRGINIA RADIOLOGICAL SOCIETY
Secretary, Dr. John M. Ratliff, Mary Immaculate Hospital, Newport News, Va.

Washington State Radiological Society

Secretary, Dr. Owen Marten, 930 Terry Avenue, Seattle, Wash. Meets quarterly.

West Virginia Radiological Society

Secretary, Dr. Karl J. Myers, The Myers Clinic-Broaddus Hospital, Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee. WESTCHESTER RADIOLOGICAL SOCIETY

Secretary, Dr. Peter P. Brancucci, Westchester Academy of Medicine, Section on Radiology, Purchase, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society

Secretary-Treasurer, Harold F. Ibach, 2400 W. Villard Ave., Milwaukee, Wis. Meets twice a year, May and September.

WYOMING RADIOLOGICAL SOCIETY

Secretary, Dr. Ronald R. Lund, 240 W. 9th St., Casper, Wyo. Meets in fall with State Medical Society and in spring on call of President.

Cuba, Mexico, Puerto Rico and Central America

ASOCIACIÓN DE RADIÓLOGOS DE CENTRO AMERICA Y PANAMA. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá. Secretary-General, Dr. Roberto Calderón, Calle Central Oeste No. 218, Managua, Nicaragua, Central America. Meets annually in a rotating manner in the six countries. Sociedad de Radiología de El Salvador

Secretary, Dr. Rafael Vaga Gómez.

Sociedad de Radiología de Guatemala Secretary, Dr. Carlos E. Escobar, 92. Calle A 0-05, Zona 1, Guatemala.

Sociedad de Radiología y Fisioterapía Cubana Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at

Curie Hospital.

Sociedad Costarricense de Radiologia Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

Sociedad Mexicana de Radiología, A.C. Calle del Oro No. 15, México 7, D. F. Secretary-General, Dr. E. Alvarez Hernández. Meets first Monday of each month.

Asociación Puertorriqueña de Radiología

Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico. Sociedad Radiológica Panamena

Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting. Sociedad Radiológica de Puerto Rico

Secretary, Dr. Jorge Carreras Girard, Suite 504, Professional Bldg., Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec Secretary, Dr. R. Robillard, Notre-Dame Hospital, 1560 Sherbrooke St., East, Montreal, Que., Canada. Meets four times a year.

BRITISH INSTITUTE OF RADIOLOGY

Honorary Secretary, Dr. R. D. Hoare, 32 Welbeck St., London, W. I, England. Meets monthly from October until May.

Canadian Association of Physicists, Division of MEDICAL AND BIOLOGICAL PHYSICS.

Honorary Secretary-Treasurer, Paul M. Pfalzner, Dept. of Therapeutic Radiology, University of Western Ontario, London, Ont., Canada. Annual meeting to be announced. Edmonton and District Radiological Society

Secretary, Dr. B. V. Evans, 105 Northgate Bldg., Alberta, Canada. Meets second Tuesday of each month in various Edmonton Hospitals.

FACULTY OF RADIOLOGISTS

Honorary Secretary, Dr. J. N. Pattinson, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting to be announced

FACULTY OF RADIOLOGISTS, ROYAL COLLEGE OF SURGEONS IN IRELAND

Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green, Dublin 2, Ireland.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)

Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, I Wimpole St., London, W. I, England.

Canadian Association of Radiologists

Honorary Secretary-Treasurer, Dr. D. J. Sieniewicz, Associate Honorary Secretary-Treasurer, Dr. Maurice Dufresne, 1555 Summerhill Ave., Montreal 25, Que., Canada. Annual meeting: Queen Elizabeth Hotel, Montreal, March 2–6, 1966.

MONTREAL RADIOLOGICAL STUDY CLUB

Secretary, Dr. Leonard Rosenthall, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française de Radiologie Secretary General, Dr. Jacques Lespérance, 1656 Sherbrooke East, Montreal, Que., Canada. Meets every third Tuesday from October to April. Annual meeting to be announced.

TORONTO RADIOLOGICAL SOCIETY

Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

COLLEGE OF RADIOLOGISTS OF AUSTRALASIA

Honorary Secretary, Dr. E. A. Booth, c/o British Medical
Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

SOUTH AMERICA

Asociación Argentina de Radiología

Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia

Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional de Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia

Secretary-General, Dr. Tede Eston de Eston, Caixa Postal 5984, São Paulo, Brazil.

Sociedad Argentina de Radiologia

Secretary, Dr. Edwarde A. Navarrine, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

Sociedad Bolivana de Radiología

Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia

Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia

Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia

Secretary, Dr. Armando Uribe, Hospital Miltar Central, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía Secretary, Dr. Luis Blum, P.O. Box 3712, Guayaquil, Ecuador

Sociedad Paraguaya de Radiología

Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia

Secretary, Dr. Vicente Ubillus, Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima. Sociedad de Radiologica del Atlantico

Secretary, Dr. Raul Fernandez, Calle 40 #4:-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física

MÉDICA DEL URUGUAY Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada

1464, piso 13, Montevideo, Uruguay. Sociedade de Radiologia de Pernambuco

Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenologia y Medicina Nuclear de

la Provincia de Córdoba

Secretary-General, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina. Sociedad Venezolana de Radiología

Secretary General, Dr. Luis F. Muro, Apartado No. 9362 Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Feceral, Caracas.

CONTINENTAL EUROPE

ÖSTERREICHISCHE RÖNTGEN-GESELLSCHAFT

President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in 9, Austria. Mieets second I destay of Allgemeine Poliklinik. Annual meeting to be announced.

Société Belge de Radiologie

General Secretary, Prof. Simon Masy, Louvain, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique Permanent Secretary, Dr. Jaques Sauvegrain, Hôpital des Enfants-Malades, 149, rue de Sèvres, Paris 15c, France. General Secretary, Dr. Ole Eklöf, P.O. Box, Stockholm 60, Sweden. Annual meeting to be announced. Société Française D'Electroradiologie Médicale,

and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, DE L'OUEST, DE L'EST, ET D'ALGER ET D'AFRIQUE DU Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.

Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 8, France.

ČESKOSLOVENSKÁ SPOLEČNOST PRO ROENTGENOLOGII A Radiologii

Secretary, Dr. Robert Poch, Praha 12, Srobárova 50, Czechoslovakia. Meets monthly except during July, August and September. Annual general meeting. DEUTSCHE RÖNTGENGESELLSCHAFT

Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut, Lagenbeckstr. 1, Mainz, Germany.
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Nederlandse Vereniging voor Radiologie

Secretary, Dr. H. F. O. Stricker, Schalklaar, Netherlands. SCANDINAVIAN ROENTGEN SOCIETIES

The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear

Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.
Schweizerische Gesellschaft für Radiologie und

Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire) Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

Indian Radiological Association

Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

INDONESIAN RADIOLOGICAL SOCIETY

Secretary, Professor Sjahriar Rasad, Taman Tjut Mutiah 1, Diakarta, Indonesia.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

HEAD

LILLY, GILBERT E., STEINER, MARTIN, IRBY, WILLIAM B., and TIECKE, RICHARD W. Oral health evaluation: analysis of radiographic findings. J. Am. Dent. A., Sept., 1965, 71, 635–639. (Address: Gilbert E. Lilly, Major, US Army, DC, Oral Surgery and Pathology Section, Research and Development Service, Letterman General Hospital, San Francisco, Calif.)

The roentgenographic features of oral studies conducted on 1,287 dentists' jaws are presented. Panoramic roentgenograms were taken as part of the Health Evaluation Program conducted at the 105th Annual Session of the American Dental Association.

Detected in the survey were: (1) 202 unerupted teeth; (2) 29 periapical radiolucent lesions; (3) 426 root canal fillings; (4) 25 retained roots and 4 foreign bodies; (5) 39 radiopaque foci which appeared to represent osteitis; (6) 8 radiolucent regions; and (7) various abnormalities of ligament or condyle areas. (8) No roentgenographic features suggested neoplasia.

It appeared that the oral health of the dentists examined was excellent.—David C. Alftine, M.D.

GLASAUER, FRANZ E. Pantopaque ventriculography—its diagnostic and prognostic value. J. Canad. A. Radiologists, June, 1965, 16, 125–131. (From: Division of Neurosurgery, State University of New York at Buffalo School of Medicine and Edward J. Meyer Memorial Hospital, Buffalo, N.Y.)

The author states that it is the purpose of his report to emphasize the diagnostic advantages, the prognostic value and the relatively innocuous nature of pantopaque ventriculography.

He describes his technique. A right frontal burr hole is made under local anesthesia, except in children where general anesthesia is preferred. With the patient prone, the neck flexed and the head slightly tilted to the side injected, the contrast medium is instilled into the right frontal horn. Without removing any fluid, 1.0 ml. to 2.0 ml. of pantopaque together with 4 ml. to 8 ml. of air is injected. Originally the "blind technique" was used but subsequently a variation of the method was substituted. whereby fluoroscopy in the lateral view was carried out and a portable roentgen-ray apparatus utilized for anteroposterior and posteroanterior spot roentgenograms. This procedure is faster and enables a more accurate filling of the ventricles, a better demonstration of the lesion and a controlled emptying of the contrast material. The technique under direct fluoroscopy can be further enhanced by

image amplification or television monitoring. In hydrocephalus, especially in infants, larger amounts of air might be used for better demonstration of the dilated ventricles, along with the I to 2 ml. of pantopaque. In cases of complete block of the aqueduct, it has been helpful to keep the patient either in the supine or sitting position for several hours and take repeat roentgenograms at various intervals, as the contrast medium may eventually pass the "block."

The author has used pantopaque as a contrast material for ventriculography in over 50 cases. He cites 4 cases demonstrating the diagnostic and prognostic advantages of repeated pantopaque ventriculography.

The recorded side effects in the use of air or pantopaque ventriculography include headaches, fever, nausea and vomiting. The temperature rarely exceeds 101°F.; headaches, nausea and vomiting are infrequent and, if present, are mild.

The author stresses the importance of using only a small amount of the pantopaque (1 to 2 ml.). He also discusses rhombencephalography in which case 9 to 12 ml. of pantopaque is used. Various other techniques are likewise discussed.

It is concluded that pantopaque ventriculography is a safe and innocuous procedure.—Peter C. Truog, M.D.

Schechter, M. M., and Zingesser, L. H. The radiology of basilar thrombosis. *Radiology*, July, 1965, 85, 23–32. (From: Albert Einstein College of Medicine, Bronx, N.Y.)

Thrombosis of the basilar artery may cause classic symptoms and signs in which case the diagnosis is quite obvious. More commonly, however, the symptoms and signs are not classic and the patient presents with symptoms and signs of a posterior fossa mass, or of vertebral-basilar insufficiency, and a search must be made for a lesion amenable to surgical therapy. It is in these patients that angiography frequently is of great help.

The signs of vertebral-basilar insufficiency in the order of frequency are: (1) disorders of equilibrium; (2) disorders of vision; (3) visceral disturbances, e.g., vasomotor, cardiorespiratory; (4) headaches (intense and usually occipital); (5) disorders of consciousness; (6) disorders of movement; (7) auditory symptoms; (8) somatic sensory problems (facial or peripheral); (9) attacks simulating migraine; and (10) convulsions.

The authors discuss the natural history of the disease vertebral-basilar insufficiency and state that the marked variability in the symptoms and the end results regarding the patient are due to the variations commonly found in the anatomy of the vertebral-basilar system and the collateral pathways found in the area.

Diagrams and roentgenograms are reproduced

showing the standard anatomy of the vertebralbasilar system and the most common variations thereof. The various routes of collateral circulation are also indicated schematically. In addition to the effects of the anatomic variations and collateral pathways, various factors relating to roentgenologic technique must also be considered in arriving at an angiographic diagnosis. Pressure-volume relationships and technique may cause streaming and laminar flow which must be differentiated from incomplete occlusion. Absence of opacification of the basilar artery without opacification of the contralateral vertebral artery, coupled with persistence of contrast material in the ipsilateral vertebral artery, may be due to technical reasons. Also, reflux of contrast material into the basilar artery from an injection into the carotid system does not necessarily mean occlusive disease in the vertebral-basilar system as this may be accounted for by pressure and volume relationships without there being occlusive disease proximally.—Donald N. Dysart M.D.

Wood, Ernest H. Thermography in the diagnosis of cerebrovascular disease. *Radiology*, Aug., 1965, 85, 270–283. (Address: University of North Carolina, Chapel Hill, N. C.)

The medically adapted thermograph is a motordriven, scanning, thermal-resistor bolometer that can be used to assess blood flow in any portion of the body by determining the temperature of that part with reference to its normal physiologic state. This paper presents the application of thermography to the diagnosis of vascular disorders, primarily of the stenotic or occlusive type, of the carotid arterial system manifested by neurologic disorders. A logical anatomic explanation for characteristic thermographic patterns is proposed and adjunctive criteria for angiography selection and evaluation of treatment are noted. The study was started by establishing cranio-facial thermographic patterns in 1,000 normal healthy subjects. The results of the diagnostic evaluation are based upon 117 patients with intra- or extracranial cerebrovascular abnormalities plus 25 patients with brain tumors and miscellaneous neurologic disorders. Every case was confirmed by angiography and/or surgery or necropsy. An over-all accuracy of 89 per cent is recorded.

The results show a pattern of medial supraorbital coolness to be characteristic of carotid insufficiency, with unilateral internal carotid occlusion giving the most striking thermographic picture. Reduced flow through the frontal and supra-orbital branches of the ophthalmic artery is the basis for this characteristic thermographic picture regardless of the level of the stenotic or occlusive process. Collateral gradient flow through the internal maxillary and superficial temporal arteries, branches of the external carotid artery, will sometimes permit a false negative examination. A false positive result can occur if the "steal phenomena" which are associated with a shunting mechanism, as in arteriovenous fistula, are present. It is noted that 50-60 per cent circulatory insufficiency is required to get a positive and diagnostic thermogram. It is also noted that insufficiency in the external carotid, middle cerebral, or vertebral systems does not produce diagnostic thermography. Successful corrective surgical procedures permit a prompt return to a negative and normal thermogram.

Thermography is presented as a quick, easy, and painless method for diagnostic screening and post-operative evaluation of patients presenting an arterial insufficiency of their common carotid and/or internal carotid arteries (proximal to the ophthalmic artery), particularly if they are suspected of having stenotic or occlusive disease.—John L. Bond, M.D.

Neck and Chest

VIAMONTE, MANUEL, JR., PARKS, RAYMOND E., and SMOAK, WILLIAM M., III. Guided catheterization of the bronchial arteries. *Radiology*, Aug., 1965, 85, 205–229. (Address: Jackson Memorial Hospital, 1700 N. W. Tenth Avenue, Miami, Fla.)

Part I-Technical Considerations.

Selective catheterization of the bronchial arteries is accomplished easily by the technique of "guided angiography" which utilizes especially constructed catheters with a minute tip, optimal torque control and tip deflection by external manipulation. During catheterization the orifices of the bronchial arteries are usually sought at slightly above the level of the left main stem bronchus between the upper border of T-5 and the lower border of T-6 vertebral bodies. The origin of the right bronchial artery is usually posterior and to the right while the left is more variable. Once the ostium is located, angiography is performed using hand injection or with an automatic injector set for "stuttering" at low pressures, so that the catheter tip is not displaced by recoil. The filming initially is accomplished with a 16 mm. cine camera after which stereoscopic roentgenograms are made on a roll-type film changer.

The number of bronchial arteries on each side varies from I to 4, but most commonly there are I or 2 arteries to the right lung and 2 to the left. The right bronchial artery frequently arises from an intercosto-bronchial trunk and is directed caudally toward the right hilus. The branches of the bronchial artery are seldom visualized beyond the medial third of the lung, except in association with some pathologic condition. The left bronchial arteries usually arise directly from the aorta, are shorter than the corresponding arteries on the right, and present a more medial course. The right and left arteries often are interconnected by mediastinal arteries, and

frequently a common bronchial trunk is demonstrated.

When the bronchial arteries are not clearly visualized in the frontal projection, roentgenograms should be obtained with the patient in the oblique and lateral positions, at which time the patient may exhibit a cough—an indication of bronchial artery filling. At times, bronchial arteries may be shown on the roentgenograms, even though they may not be recognized on the television monitor. Also, a pitfall in interpretation may arise from the fact that more than one bronchial artery may supply each lung, especially the left side. Unless one injects the bronchial artery supplying the lesion under study, one should not conclude that the tumor receives no blood from the bronchial artery system.

All of the studies performed by the authors, to date, have been under local anesthesia, but a similar investigation is being planned under general anesthesia in hopes of permitting the use of larger amounts of contrast medium. While spinal cord damage is a theoretic hazard because of spinal artery branches from intercostal arteries, symptoms of neurotoxicity were not encountered in this study. At present, the use of vasodilators and selective injection of radioactive scanning materials during selective angiography is being evaluated.

Part II-Pulmonary and Mediastinal Neoplasms.

Fifty-five cases of malignant pulmonary neoplasms were studied by selective bronchial arteriography using the "guided angiography" technique and the abnormal vascular patterns observed were classified in 5 abnormal forms: (1) localized hypervascularity in or adjacent to the neoplasms with either a "tumor blush," an increased number of small branches in the tumor, or ectatic or irregularly distributed fusiform vessels; (2) a "sequestered" form in which there is preferential flow of blood to a hypervascular neoplasm; (3) an aberrant or dual vascular supply with an additional blood supply from other arteries such as the intercostal or internal mammary arteries; (4) an avascular pattern; and (5) bronchial hypervascularity of seemingly uninvolved lung parenchyma, appearing normal on plain roentgenograms and on laminagraphy, but later shown to be involved with tumor.

In primary pulmonary cancers the bronchial arteries seek the tumor regardless of its location. Those supplying bronchogenic carcinoma may appear normal or slightly enlarged and their branches surround the lesion or penetrate the tumor. The degree of vascularization is unpredictable and variable. In the great majority of squamous cell carcinomas, a paucity of bronchial arteries supplying the tumor has been the most common observation and the tumor vessels are in general pleomorphic and exhibit abnormal dynamics. Magnification roentgenography provides the best means for analysis of the tumor vascularity.

The degree of vascularity of primary pulmonary neoplasms may prove an important factor in predicting response to radiotherapy. This feature is under evaluation as well as the effect of chemotherapeutic agents infused into the bronchial artery following angiography. The experience of the authors indicates that the diagnostic evaluation of a pulmonary mass cannot be determined on the bronchial angiographic findings exclusively. The differentiation of benign from malignant tumor may ultimately depend on detailed morphologic analysis and the pharmcodynamic behavior of small vessels rather than on the evaluation of the size, number, and distribution of the opacified vessels.

Part III—Nonmalignant pulmonary and mediastinal pathologic conditions.

The respiratory tract can be divided into the bronchiolized and alveolized regions which are embryologically, anatomically, and functionally different but at the same time interdependent. The bronchiolized region, extending from the trachea to the respiratory bronchiole, is an air-conducting, fluid-secreting structure supplied by the bronchial arteries, while the alveolized region comprises respiratory units beyond the respiratory bronchiole and is supplied by the pulmonary arteries. Alteration in either circulation may influence the status of the other and various patterns of bronchial hypervascularity have been demonstrated following pulmonary arterial occlusion and in inflammatory pulmonary and mediastinal diseases. In the cases observed by the authors, bronchial hypervascularity was especially prominent in the central portion of the lungs. In the presence of severe pulmonary arterial hypertension, the bronchial arteries are noted to be of small caliber. This diminution in size may be related to the markedly increased pressure in the pulmonary artery or possibly related to a high flow resistance, co-existing in the pulmonary and bronchial arterial beds.

Inflammatory processes such as pneumonitis, abscess, sarcoidosis, and tuberculosis may show variable degrees of bronchial vascularity. Bronchiectasis may cause striking alterations in the morphology and hemodynamics of the bronchial arterial circulation but there has been no correlation between the appearance of the bronchi and the degree of bronchial hypervascularity which is problably related only to the activity of the inflammatory changes in the walls of the bronchi. Generally, in any case with markedly augmented bronchial flow, a filling and reversal of flow in branches of the pulmonary artery may be observed. The demonstration of large bronchial arteries, marked by hypervascularization and/or bronchopulmonary anastromoses, should suggest a benign process.

Granulomas and hamartomas are usually avascular lesions, while solitary nodules receiving blood supply from the bronchial arteries should be considered as candidates for biopsy or resection because of the likelihood of their being a primary or metastatic cancer. A disappointment has been the demonstration of metastatic avascular lesions and hypervascular inflammatory pulmonary nodules. Mediastinal nonvascular processes have also been studied with bronchial arteriography but prominent vessels arising from bronchial arteries and/or aortic intercostal arteries and supplying mediastinal lymph nodes have been observed in both inflammatory and malignancy lymphadenopathies.

The authors admit to a limited experience in nonmalignant conditions but they consider benigh those lesions that show several of the following: markedly enlarged bronchial arteries, extensive broncho-pulmonary anastomoses and normal branching appearance, gradual tapering, and uniform distribution of smaller branches of the bronchial artery. In contrast, pleomorphism and altered dynamics are features of tumor vascularity.—Edward B. Best, M.D.

STECKEN, A. Das "figure of eight" Syndrom im Schul- und frühen Erwachsenenalter und seine Differentialdiagnose. (The differential diagnosis of the "figure of eight" syndrome in school children and young adults.) Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin, June, 1965, 102, 626-645. (Address: Röntgeninstitut, Marienstr. 2, 8670 Hof/Saale, Germany.)

The "figure of eight" is due to total anomalous pulmonary venous drainage with a persistent left superior vena cava. The average age attained by these patients is 1.8 years. Survival depends on the existence of an inter-atrial septal defect and the resistance in the pulmonary circulation. A large septal defect associated with short and broad pulmonary channels increases the life expectancy of these individuals. In this anomaly, the right pulmonary veins merge into a common channel posterior to the heart on the left side where they unite with the left pulmonary veins at the level of the left atrium or in the hilar region. From there, a common trunk proceeds in a craniad direction anterior to the pulmonary main stem or between this and the main bronchus (in the latter instance, the bronchus may become compressed). The left mediastinal border is due to the persistent left superior vena cava. A true persistence exists when the Cuverian duct as well as the left cardinal vein remains open. If the duct is transformed into the coronary venous sinus, while the inferior portion of the cardinal vein becomes obliterated, then the condition is one of partial persistence.

The diagnosis is made chiefly on the basis of tomography. An adequate study requires a minimum of 4 tomograms in each of the following projections:

anteroposterior, left lateral and right lateral, simultaneously. Kymography aids in the presence of aortic aneurysms or double aortic arch. Angiocardiography is necessary to determine the existence of other anomalies. The tomographic findings are as follows: (1) In the anteroposterior view, the right venous trunk can be followed more medial than usual and above the normal entry level at the right border of the left atrium; an atypical, vertical venous stem is noted in the left hilus; somewhat more anteriorly, the supracardiac biconvex enlargement can be seen. (2) In the right lateral view, the widened superior vena cava is clearly seen; also, the retrocardiac venous trunk is located below the right main pulmonary artery between the posterior wall of the heart and the spine; there is no indentation on the posterior cardiac wall since the right pulmonary veins do not enter the left atrium. (3) In the left lateral view the persistent left superior vena cava produces a wide shadow; the left pulmonary vessels enter at the base of this wide vessel. In addition to these features, this anomaly is associated with pulmonary hypervascularity.

In the differential diagnosis, neoplasms rarely offer any problem since the lungs show no hypervascularity and the tomograms disclose a normal venous circulation. Furthermore, neoplasms frequently have a nodular configuration and are seen anterior and/or posterior to the trachea; the anterior mediastinum, if involved, is entirely obscured by the tumor, whereas in the venous anomaly it is clear and the smoothly contoured superior vena cavae are recognized by a linear or slightly ventral bowing; in the anteroposterior tomogram, normal veins end in the right paravertebral region despite the neoplasm; in the left lateral tomogram, a normal venous relationship is seen as well as a normal pulmonary oval.

A variety of vascular anomalies can be distinguished from the "figure of eight" syndrome:

- 1. Partial communication of left pulmonary vessels with distal persistent left superior vena cava. In this condition, the retrocardiac venous trunk is absent.
- 2. Partial communication of left pulmonary vessels with right pulmonary veins entering the right superior vena cava. The retrocardiac trunk is absent. The veins of both upper lobes have an atypical course while those from the lower lobes are normal.
- 3. Partial anomalous communication of left pulmonary veins with distal persistent left superior vena cava combined with mitral stenosis and tricuspid insufficiency. The right pulmonary veins are normal and there is no retrocardiac trunk.
- 4. Right-sided cardiac insufficiency with persistent left superior vena cava and normal pulmonary veins. There is a smooth dilatation of the left supracardiac shadow but the retrocardiac trunk is absent.
- 5. Aortic aneurysm. The venous circulation is normal.

- 6. Double aortic arch. The biconvexity is smaller and narrower. The venous flow is normal.
- 7. Transposition of the great vessels. Pulmonary vascularity is decreased. Angiocardiography is diagnostic.—J. Zausner, M.D.

RADIATION THERAPY

HOLSTEN, D. R. Hilfsmittel für die Telekobalttherapie. (Accessories for telecobalt therapy.) Röntgen Blätter, March, 1965, 18, 127–134. (From: Univ.-Strahlenklinik, Marburg/ Lahn, Germany.)

The author describes methods and devices for: (a) directing and limiting cobalt therapy fields; (b) measuring radiation doses with intracavitary dosimeters; (c) protecting sensitive tissues from the radiation beam, e.g., the eye's lens; and (d) the use of compression cones during cobalt therapy.—Henry G. Mochring, M.D.

THOMAS, E. D., EPSTEIN, R. B., ESCHBACH, J. W., Jr., PRAGER, D., BUCKNER, C. D., and MARSAGLIA, G. Treatment of leukemia by extracorporeal irradiation. New England J. Med., July, 1965, 273, 6–12. (From: Department of Medicine, University of Washington School of Medicine, and the Boeing Scientific Research Laboratories, Seattle, Wash.)

Modern concepts of the true nature of lymphocytic leukemia have been undergoing considerable change. Whereas at one time leukemia was thought to be a disease in which abnormal cells crowded out normal ones by intense and rapid proliferation, it is now felt that leukemia is a matter of the development of large populations of abnormal cells because of the excessively long life of the leukemic cell. Studies of the incorporation of tritiated thymidine indicate that very few cells of a leukemic population are in mitosis at any one time, a fact which strongly supports the new theory. Several groups have approached the treatment of leukemia with an attempt to deplete stores of abnormal cells by constantly removing leukemic cells from the peripheral circulation by extracorporeal irradiation of the blood stream. It is hoped that abnormal cells will prove more radiosensitive than normal ones, and that removal of abnormal cells from the circulation will be a stimulus for the release of replacement abnormal cells from marrow, spleen and other storage sites. If this method worked as well in fact as in theory it would lead to the eventual disappearance of abnormal cells, which might be equated with cure of the disease.

The authors' irradiation system makes use of silastic-teflon shunts which are placed between an artery and a vein in the patient's forearm. While in transit through this shunt the blood receives radiation from one of a number of orthovoltage radiation

sources which deliver doses in the radiation field of from to 2,000 r to 5,000 r per minute. In general, extracorporeal irradiation is carried out during periods of from 2 to 8 hours. Doses delivered vary widely, for they are a function of many factors including transit dose, flow rate and the volume of blood in the irradiation field. By the authors' calculations the cumulative mean dose to red blood cells which were in circulation throughout the period of extracorporeal irradiation may fall within a wide range of from 900 to 27,000 r.

Results in the application of this technique are appraised in 5 cases, and in only I of these did a genuine remission appear to have been produced. In several of the other cases there was a definite suggestion that the abnormal cell population may have become resensitized to a chemotherapeutic agent to which it had previously become resistant. In any case, this interesting method, which has also been applied to the problem of homograft rejection, does not appear to be the definitive treatment for lymphocytic leukemia, but does seem to be one which deserves further study.—Frederick J. Bonte, M.D.

Borghi, A., and Mainoldi, F. Le metastasi ossee da neoplasia uterina. (Bone metastases from uterine neoplasm.) Radiobiol., radioter. e fisica med., Jan.—Feb., 1965, 20, 28–56. (From: Istituto di Radiologia dell'Università di Bologna, Italy.)

The authors have reviewed all the cases of uterine neoplasm treated since January 1, 1960 at the Radium Institute of the University of Bologna.

Seven-hundred-thirty-two patients presented epithelial neoplasms of the cervix or of the cervical canal; in 84 the lesion involved the body of the uterus; and in 12 the neoplasm proved to be a sarcoma of the body of the uterus.

Skeletal metastases were found in 32 cases, an incidence of 4.3 per cent. Of these cases, only in 2 (0.64 per cent) was the primary lesion located in the body of the uterus.

In 16 individuals the primary lesion was classified as Stage 1; in 7 as Stage 11; in 7 as Stage 111; and in 2 as Stage 11. Of the 32 patients, only 6 were subjected to Wertheim procedure before being treated by radiotherapy.

Histologic studies of the metastatic foci were not very characteristic. The neoplastic cells showed a great tendency to infiltrate the bone trabeculae with marked osteoclasis of the mesenchyma.

Roentgenologically the osteolytic foci were generally isolated, but in rare cases were disseminated. Infrequent was the mixed form, osteolytic and osteoblastic, and even more rare the osteoblastic type.

The pelvic bones were involved, with or without other secondary foci, in 24 cases; the lumbar vertebrae in 7 (with 3 individuals also presenting

metastases to the pelvic bones and humeri); the skull in 2 cases; the thoracic spine in 1 case; and the humerus in 1 case.

The time of appearance of the metastases, from the completion of the radium treatment, appeared to be rather early. In 14 cases, (43 per cent) metastases were demonstrated roentgenologically within I year and even earlier.

The survival after the appearance of the metastases was poor: 6 months in 16 cases (50 per cent); more than 1 year in 8, of which 5 cases were still alive 2 years from the discovery of the secondary focus; in the remaining 8 patients still alive, the metastases have been present only from 2 to 6 months.

Quite rare was the localization in other systems. Four cases presented lung metastases, while in single cases the secondary foci were located in the hypophysis, liver, skin and inguinal lymph nodes. Frequently noted were an associated infiltration of the floor of the pelvis, involvement of the rectovaginal septum, and extension to the deep lymphatic chain of the pelvis.

The metastases were considered secondary to hematogenous or lymphatic spread, or to a localization by contiguity. The lymph borne metastases were the most frequent; only in 8 cases was the secondary lesion thought to be bloodborne. Metastases to the area of the innominate bone were by contiguity, following infiltration from an involved lymph node.

The roentgen treatment of the skeletal metastases gave rather poor results and was considered only as a palliative therapeutic measure. A partial recalcification of an osteolytic process with regression of the related symptomatology was noted only in 2 cases.—

A. F. Govoni, M.D.

LINSCHEID, RONALD L., SOULE, EDWARD H., and HENDERSON, EDWARD D. Pleomorphic rhabdomyosarcomata of the extremities and limb girdles; a clinicopathological study. J. Bone & Joint Surg., June, 1965, 47-A, 715-726. (Address: 200 First Street, S. W., Rochester, Minn. 55902.)

A preliminary review of 1,373 somatic soft-tissue sarcomata at the Mayo clinic revealed 9.1 per cent of them to be pleomorphic rhabdomyosarcomata. Eighty-seven rhabdomyosarcomata of the extremities and limb girdles were reviewed.

It was found that tumors located within individual muscles or between muscles developed rather distinct pseudocapsules, while superficial tumors tended to have less of a pseudocapsule.

Patients ranged in age from 14 to 89 years, the median age being 55 years. There were 53 males and 34 females.

The tumor was located in 54 per cent of the cases

in the upper extremity and 46 per cent in the lower extremity.

The presenting complaint in 68 per cent of the patients was a painless mass. In 25 per cent, pain in the involved extremity or radicular pain was the presenting symptom. In the remaining cases, symptoms other than mass or pain were noted initially.

The average duration from time of onset of symptoms to diagnosis was 8.1 months.

In 28 patients, the roentgenographic findings were: soft tissue density in 15; periosteal reaction in 5; and lytic bone destruction in 8.

Treatment was divided into 4 categories: biopsy and irradiation; local excision; radical en bloc excision; and amputation.

Irradiation and biopsy were used in 3 patients, all of whom had demonstrable metastases when they were first seen for treatment.

Of the 30 five-year survivors, 24 had either amputation or radical en bloc excision. Difficulty in eradicating rhabdomyosarcomata by local excision was demonstrated by the fact that 134 recurrences were noted in 59 patients.

Thirty patients survived 5 years or longer from the time of surgical treatment; of these, 12 survived 10 years or longer.—Forrest Arnoldi, M.D.

Fraser, Russell. Hypercalcaemia and hypoglycaemia associated with tumours. *Proc. Roy. Soc. Med.*, July, 1965, 59, 483–485. (From: Postgraduate Medical School of London, London, England.)

Hypercalcemia was initially noted occasionally with widespread bone metastases, but has now been documented as occurring with a variety of tumors, particularly hypernephromata and bronchial carcinomata, without demonstrable bone metastases. This suggests that there is a humoral factor coming from the tumor, since removal of the tumor has been observed in many instances to be followed by loss of the hypercalcemia. Most hypercalcemias due to nonparathyroid tumors, including sarcoid, will respond to cortisone treatment, thus helping to distinguish from true hyperparathyroidism, and also aid in the initial relief of symptoms.

With a rise in serum calcium the onset of symptoms is insidious, the patient experiencing an initial vague tiredness and listlessness. This is progressively followed with headache, nausea, and vomiting, and perhaps some degree of polyuria. The next steps are confusion, suggesting cerebral metastases, and fever from dehydration, suggesting infection. Progressive uremia stimulates the development of a secondary hyperparathyroidism which complicates the picture.

Hypercalcemia or hypercalcuria can sometimes offer a good guide to the success of treatment, but only if these values are abnormal before the treatment. This humoral factor may also play a part in

producing the hypercalcemia that is associated with known bone metastases.

Hypoglycemia is a more rare complication associated with other tumors, namely hepatomata and mesotheliomata. This side effect of hepatomata is encountered almost exclusively in Hong Kong and often complicates cirrhosis. The mechanism by which hepatomata and mesotheliomata produce this hypoglycemia is still in doubt, with the author's evidence favoring the view that the tumors stimulate the subject's own pancreatic insulin production. He has been unable to extract more insulin from these tumors than from the patient's other tissues. He has noted that glucose tolerance tests may take months to return to normal following removal of these tumors, suggesting that the islet cells are hyperplastic and cannot easily settle down to quiescence even though the tumor and its stimulating substance have been removed. No evidence could be found that this substance was leucine, although it might be a similar substance. Further studies are needed.— Donald M. Monson, M.D.

Ross, E. J. Endocrine and metabolic consequences of carcinoma of the bronchus. *Proc. Roy. Soc. Med.*, July, 1965, 58, 485–487. (From: University College Hospital Medical School, London, England.)

Undifferentiated cancer cells, such as found in oat cell carcinoma of the lung, have been shown to have the ability to produce polypeptides which are physiologically active. If these substances are not chemically identical with the natural hormones, they at least have biologic properties identical with them. Corticotrophin, parathormone, antidiuretic hormone, serotonin, thyroid stimulating hormone and gonadotrophin have all been identified within these undifferentiated tumors by biologic or immunologic methods.

The corticotrophic (ACTH) activity produces bilateral adrenocortical hyperplasia with high plasma concentration of corticoids. Rarely do the patients exhibit the clinical features of Cushing's syndrome, probably because of their early demise. They may develop, however, edema of the legs, diabetes, and hypokalemic alkalosis. There are conflicting reports whether injected corticotrophin can further stimulate release of additional corticoids. A shorter survival has been noted by some with greater responses in the production of 11-hydroxycorticoids. Corticotrophin production is most commonly seen in oat cell carcinoma of the bronchus, thymus, pancreas and ovary, but has been found in a wide variety of malignancies.

Parathormone activity with its resultant hypercalcemia, hypophosphatemia and hypercalcuria, and the clinical features of polyuria, thirst, constipation and mental confusion, has been detected even in the absence of demonstrable bone metastases. Removal or irradiation of the tumor results in a fall of plasma calcium concentration to normal, with a rise if metastases appear. Neoplasms commonly associated with this activity are oat cell carcinoma of the lung and hypernephroma, but it has also been reported with carcinoma of the ovary, pancreas, uterus, colon and breast.

The antidiuretic activity results in a dilutional hyponatremia that can be differentiated from Addison's disease by the absence of hemoconcentration and extrarenal uremia, and by the blood pressure usually being slightly elevated. These patients are frequently drowsy, sometimes disorientated and occasionally pigmented. There has been some evidence reported, however, which suggests that patients with dilutional hyponatremia appear to survive longer than would be expected. This complication occurs in oat cell carcinoma, as well as in other non-neoplastic cerebral and lung diseases.

Serotonin may also be secreted by adenomata and occasionally by oat cell carcinomata, in addition to the more characteristic argentaffin tumors of the gastrointestinal tract. The typical carcinoid syndrome may result.

Some findings of hyperthyroidism have been detected, such as elevated protein bound iodine, tachycardia, eye signs and tremor, but none had a goiter.

The neoplasms involved include those originating in the bronchus, gastrointestinal tract, prostate, embryonal carcinoma of the testis, and choriocarcinoma. There seems to be a particularly close association between trophoblastic tumors and hyperthyroidism.

Red blood cell aplasia resulting in severe anemia has been reported most commonly in association with thymoma, but has also been seen with carcinoma of the bronchus. The plasma contains a substance capable of depressing iron utilization in rabbits.

Neurologic complications may of course be produced by cerebral metastases. Peripheral neuritis, myopathy with myasthenic characteristics, and cerebellar atrophy, however, may occur in the absence of metastases. The signs may develop 2–3 years before the manifestations of malignancy appear. These complications have been most common in patients with carcinoma of the bronchus but have also been encountered with carcinoma of the breast, uterus, ovary, stomach, and prostate.

The conclusions drawn suggest that as these complications are more carefully sought out and corrective therapy instituted, the higher the reported incidences will be and the more comfortable the patient will be in the terminal phases of his disease. As these polypeptides may not only give early clues to diagnosis, but also appear to have some influence on the prognosis, the study of the effects of these polypeptides on the rate of progression of cancer

may throw some light on the factors influencing tumor growth.—Donald M. Monson, M.D.

Penington, D. G. Polycythaemia in neoplastic diseases. *Proc. Roy. Soc. Med.*, July, 1965, 58, 488-490. (From: London Hospital, London, England.)

Polycythemia secondary to hypoxia, and polycythemia vera are both well known entities. The former is characterized by increased production of red blood cells without changes in white blood cells, platelets, or the myeloid reticulum stroma, while the latter is distinguished by splenomegaly, an increase in the circulating white blood cells and platelets, an elevated alkaline phosphatase, and a not infrequent termination in an acute leukemia.

Polycythemia or erythrocytosis has now been described with a variety of renal abnormalities (carcinoma, adenoma, hydronephrosis, cyst), as well as with cystic hemangioblastoma of the cerebellum, massive uterine fibroid, hepatoma, hamartoma of the liver, and pheochromocytoma. The mechanism of increased red blood cell production in these cases, as well as in hypoxic polycythemia, is apparently by an increase in production of the physiologically normal erythropoietin. This hormone is a mucoprotein and its action on the bone marrow is to stimulate normoblast proliferation, having no effect on leukocyte or platelet production. Studies suggest that the kidney, and more specifically, the renal tubular epithelium, is the major site of production in the body under conditions of anemia. Removal of the offending tumor is usually followed by a complete remission of the erythrocytosis.—Donald M. Monson, M.D.

RADIOISOTOPES

Arborelius, J., Jr. Kr⁸⁵ in the study of pulmonary circulation during bronchospirometry. Scandinav. J. Clin. & Lab. Invest., 1965, 17, 253–256. (From: Laboratory of Clinical Physiology, Allmänna Sjukhuset, Malmö, Sweden.)

The purpose of this report is to compare the conventional oxygen uptake technique with the krypton 85 technique for the determination of the relative circulation and ventilation of the lungs during bronchospirometry. More than 95 per cent of the Kr⁸⁵ injected intravenously leaves the blood at the first passage through the lungs and thus the amount of Kr⁸⁵ exhaled from each lung during bronchospirometry is directly proportional to the blood flow.

Kr86 was dissolved in saline solution and was injected intravenously and the expired gas was collected during the time needed for the N₂ washout from the lungs during oxygen breathing. The injected Kr86 is eliminated at the same rate as the N₂. The bronchospirometry was performed with a

Carlen's catheter. The oxygen concentration in the double spirometer was 40 per cent. The exhaled gases from each side were collected in Douglas bags. The exhaled volume was measured with a wet gas meter, and the radioactivity of the mixed gas in the bag was determined with a Geiger-Müller tube.

Twenty-three patients with different lung diseases and 10 healthy volunteers were studied. The methodologic error estimated from duplicate determinations was less with the Kr⁵⁶ technique than with the conventional method. The relative circulation and ventilation were almost identical.

The Kr⁸⁵ technique is independent of O₂ and CO₂, and should be of value in investigating the influence of changes in the concentration of these gases in the pulmonary blood flow.—C. W. Cooley, M.D.

OLDENDORF, W. H., KITANO, MASAMI, and SHIMIZU, SHIRO. Evaluation of a simple technique for abrupt intravenous injection of radioisotope. J. Nuclear Med., March, 1965, 6, 205–209. (From: The Neurology Section, Medical Service, Wadsworth Hospital, Veterans Administration Center, Los Angeles, Calif., and Division of Neurology, Department of Medicine, UCLA Center for the Health Sciences, Los Angeles, Calif. 90024.)

Abrupt intravenous injection of a labeled compound is a prerequisite of several techniques for hemodynamic evaluation.

To deliver a tracer to the right heart rapidly, the authors first placed the subject's arm on a slightly elevated armboard with the elbow slightly flexed. A Velcro blood pressure cuff was placed on the upper arm and inflated to 10 mm. of mercury, provided that this was below the systolic brachial pressure. In approximately I minute, venous distention occurred with a rise in venous pressure to exceed the cuff pressure. A 25 gauge, I inch needle was placed in the antecubital vein for subsequent injection. The cuff pressure was then increased to exceed the brachial systolic pressure. Thus, circulation in the distal arm was cut off with distention of the venous pool. Up to 3 ml. of solution could then be injected without significant extravasation. With an abrupt release of the cuff the tracer was delivered rapidly to the right heart.

To evaluate this procedure, 10 subjects were studied utilizing the abrupt cuff release technique to measure the arrival of the tracer in the head. Subsequently, the subjects were studied utilizing a rapid injection technique with a 20 gauge needle.

The plot of the results revealed that in the abrupt cuff release technique, there is a shorter arm to head circulation time. The head count also rises to a higher, sharper peak and falls off more rapidly.—Forrest Arnoldi, M.D.

Gorten, Ralph J. The use of ¹²⁶iodine for precordial counting. J. Nuclear Med., March, 1965, 6, 169–174. (From: Radioisotope and Medical Services, Veterans Administration Hospital and Department of Medicine, Duke University Medical Center, Durham, N. C.)

This study is, to the author's knowledge, the first evaluation of the use of I¹²⁵ albumin and small uncollimated detectors for determination of cardiac output.

Utilizing a miniature scintillation detector with a wafer crystal placed over the precordium and attached to a conventional linear ratemeter and a milliammeter, 20–40 μ c of I¹²⁶ albumin was injected intravenously. Well-defined curves were obtained and compared with curves utilizing I¹³¹.

The results of the comparison in 16 patients, including some with heart disease, revealed a high degree of correlation in measured cardiac output values.

Two advantages of I¹²⁶ over I¹³¹ are a longer storage life and a lower radiation exposure with comparable doses.—Forrest Arnoldi, M.D.

LOCKNER, D. A method for the simultaneous liquid scintillation counting of Fe⁵⁵ and Fe⁵⁹ in blood samples. *Scandinav. J. Clin. & Lab. Invest.*, 1965, 17, 247–252. (From: Isotope Division, Department of Alcohol Research, Karolinska Institute, Stockholm, Sweden.)

Fe⁵⁵ and Fe⁵⁹ have been used simultaneously in the study of iron metabolism. Fe⁵⁹ is easily measured due to its strong beta and gamma radiation. Fe⁵⁵ is difficult to measure due to its low energy electron capture radiation of .0059 mev. Several time-consuming methods have been used to measure both Fe⁵⁵ and Fe⁵⁹.

The author presents a method which allows the measurement of Fe⁵⁵ alone, or in a mixture with Fe⁵⁹ in blood or plasma samples without any sample preparation. The samples are directly pipetted on disks of filter paper which, after drying and without further manipulation, were counted in a liquid scintillation counter.

Counting efficiencies of 12.8 per cent (Fe⁵⁸) and 100 per cent (Fe⁵⁹) were obtained for plasma and of 3 per cent (Fe⁵⁹) and 42.9 per cent (Fe⁵⁹) for blood.— C. W. Cooley, M.D.

Avioli, Louis V., Cracco, Roger Q., and Chambers, Richard. 203 Mercury brain scans: the use of small doses as a screening method. J. Nuclear Med., April, 1965, 6, 252–264. (From: Division of Neurology and Research Isotope Laboratory, New Jersey College of Medicine, Jersey City, N. J.)

A dose of 3 to 5 μ c/kg. of Hg²⁰⁸ neohydrin was

administered intravenously 2 to 3 hours before commencement of the brain scans. This represents approximately one half the usual dose of this isotope used for a brain scan.

Of the 150 patients included in the study, 52 had abnormal brain scans. Of this group, 39 were patients with neoplasms, 2 each with abscesses, chronic subdural hematoma and hydrocephalus and 1 each with angioma, aneurysm, subarachnoid hemorrhage, hypertensive intracerebral hemorrhage, multiple sclerosis and lead encephalopathy.

Of the 98 patients with scans which were reported as normal, there were 12 who had intracranial tumors. In that total series, 51 patients had brain tumors, of which 39 were correctly localized. This represents a 76 per cent accuracy, comparing favorably with other reported series.

The authors believe that the use of the smaller dose of Hg²⁰³ neohydrin provides an adequate screening procedure for patients suspected of having brain pathology. They point out the necessity of obtaining scans in several projections of the head in order to make the correct diagnosis.

A point worth mentioning concerning their technique is that the scanning speed used was 18 cm. per minute. This is approximately one half of the speed which is usually employed and should, therefore, provide results which are as reliable as those reported by others. If scans in 4 projections of the skull are to be obtained at this rather slow speed, more than 2 hours would be required per patient study which seriously limits the number of patients which might be scanned during the working day.—

Merle Loken, M.D.

VOLPÉ, ROBERT, ROW, VAS V., WEBSTER, BRIAN R., JOHNSTON, MACALLISTER W., and EZRIN, CALVIN. Studies of iodine metabolism in Hashimoto's thyroiditis. J. Clin. Endocrinol. & Metabol., May, 1965, 25, 593-601. (From: Department of Medicine, University of Toronto, Toronto, Ontario, Canada.)

The rate of recognition of Hashimoto's thyroiditis has greatly increased in the past few years, in part due to the use of immunologic tests and needle biopsy. The current view is that Hashimoto's disease might represent an "auto-immune" lesion. In the present study, the authors report certain alterations of iodine metabolism observed in 9 patients with Hashimoto's disease.

Patients were studied primarily by chromatographic analyses of thyroid tissue and serum. The results defined a group of metabolic defects frequently observed in many cases of Hashimoto's disease. These defects are not consistently present in every patient, and when present may vary in degree.

The antithyroglobulin titers were high but the correlation with the complement fixation test result

was only fair. In 3 patients with high thyroidal I¹³¹ uptakes, the potassium perchlorate "flushing" study demonstrated an apparent defect in the organic binding of iodine. There was elevation of the I¹³¹ protein-bound iodine but there was not a corresponding elevation in the butanol-extractable I¹³⁷ values. The chromatograms of the thyroid tissue were abnormal in every patient. There was an abnormal increase in the MIT/DIT ratio demonstrated by both I¹³¹ and I¹³⁷ methods. The needle biopsies of the thyroid gland presented the histologic appearance of Hashimoto's disease.

The causes of the various abnormalities demonstrated are speculative. Each defect is not consistently present in every patient and it is probable that the defects are secondary to the tissue injury and are thus not specific for Hashimoto's disease.—Millard N. Croll, M.D.

Holmquist, B., and Alffram, P.-A. Prediction of avascular necrosis following cervical fracture of the femur based on clearance of radioactive iodine from the head of the femur. *Acta orthop. scandinav.*, 1965, 36, 62–69. (From: Orthopaedic Research Laboratories, and Orthopaedic Clinic, Malmö Allmänna Sjukhus, University of Lund, Malmö, Sweden.)

To this day avascular necrosis of the femoral head remains the principal cause of nonunion of cervical fractures of the femur. There are a number of experimental methods for predicting viability of femoral head, and several involving radioactive tracers have been described in the past.

The authors' method involves the intraosseous injection of I131, presumably as iodide, by means of a specially designed cannula. Ten microcuries of activity in no more than 0.1 ml. of solution were injected, and 5 minutes were allowed for pressure equilibration to occur. The level of radioactivity in the femoral head was then recorded by means of an external counting system, and, as might be expected, slow disappearance rates were encountered in heads the vascularity of which was impaired. A more rapid fall of activity was encountered in femoral heads whose blood supply was essentially intact. A decline in radioactivity between 5 and 15 minutes after injection of less than 5 per cent has a considerable prognostic value, for in 8 of 11 cases in which such a value was obtained aseptic necrosis of the femoral head developed as a complication of treatment and healing. Only one of 14 femoral heads which demonstrated a disappearance rate above 5 per cent showed evidence of femoral head necrosis.

This experimental isotope procedure showed an apparent prediction accuracy of 84 per cent, and is probably worth considering as a test method by laboratories working on this problem.—Frederick J. Bonte, M.D.

Benoit, Frederick L., and Durrance, Frederick Y. Radiothyroxine turnover in obesity. Am. J. M. Sc., June, 1965, 249, 647-653. (From: Clinical Investigation Center and Radioactive Isotope Branch, Radiology Service, U. S. Naval Hospital, Oakland, Calif.)

Because obese patients were usually found to have lowered metabolic rates in association with normal protein bound iodine and I'm uptake value, 10 obese active duty Naval personnel were evaluated in an attempt to discover whether or not there was a block in the cellular utilization of the primary thyroid secretory product, a defect in the peripheral metabolism of thyroxine. The patients were given 40 to 50 μc of l-thyroxine I¹³¹ intravenously; serum specimens were drawn daily for I week; and all samples were counted at the conclusion of the study. From these data the authors were able to determine the biologic half-life and the turnover rate of radiothyroxine, also the extrathyroidal organic iodine pool and the thyroxine degradation rate. The butanol extractable iodine and thyroxine-binding globulin levels were also obtained on each patient.

The authors expected to find a retarded turnover rate in obesity. What they actually found was that as relative obesity increased, the thyroxine half-life decreased, with a consequent more rapid turnover. It was postulated that this apparent rapid turnover of thyroxine could be caused by increased excretion of the hormone via the liver and gastrointestinal tract. Numerous studies in man and animals were cited to confirm that thyroxine is localized in the liver and excreted through the bile duct into the feces. No measurements of stool radioactivity were made during the course of this study; thus the authors were unable to confirm their theory. Nevertheless, they were able to confirm that there was no significant change in the extrathyroidal organic iodine pool or the hormonal degradation rate.-Kenneth M. Nowicki, M.D.

Jadresic V., Alfredo, Poblete, Mario, Reid, Alexander, Riera, Melchor, Matus, Aurora, and Herreros, María. Therapeutic hypopituitarism induced by stereotaxic transfrontal implantation of yttrium-90 in patients with breast cancer. J. Clin. Endocrinol. & Metabol., May, 1965, 25, 686–697. (From: University of Chile Medical School, Departments of Medicine, Pathology, and Radiology, Hospital San Juan de Dios, and Department of Surgery, Hospital Psiquiatrico, Santiago de Chile, Chile.)

Numerous reports regarding destruction of the hypophysis by the placement of radioactive material in the sella turcica transnasally have been made, and these have confirmed the usefulness of the method for ablation of the pituitary gland. The authors report their experience with 43 patients with far advanced breast malignancy who were submitted to stereotaxic transfrontal implantation of yttrium 90 seeds under local anesthesia. There were no immediate deaths from the procedure and 4 patients were implanted twice.

In the early days of the study, 19 patients had implantations using seeds with a total dosage of 7.1 to 15.5 mc. Three of these showed visual damage related to the high location of the pellets within the sella turcica. The remaining 24 patients received seeds with the total dosage of 18.0 to 23.4 mc placed deeply in the floor of the sella turcica with no ensuing visual damage. There was no active selection of patients, the age varying from 29 to 70 years although all showed extensive spread of the disease and were considered inoperable. Following the operative procedure, all patients received cortisone and penicillin for 2-3 days and were subsequently maintained on 37.5 mg. of cortisone daily. Rhinorrhea was a complication in 8 patients, ceasing spontaneously in 3 and associated with meningitis

The higher percentage of prolonged remissions was observed in those patients who presented hypopituitarism (35 per cent), while those who showed persistent pituitary function demonstrated only a 20 per cent remission. Significant subjective improvement was observed in 74 per cent of the patients with pain relief occurring in 88 per cent in whom pain was a major factor before implantation.

Objective remission of metastasis from the breast malignancy lasting more than 6 months occurred in 27 per cent of the total series and in 35 per cent of the patients with complete hypopituitarism.

Complications from the procedure were visual damage, rhinorrhea, and diabetes insipidus with minor episodes of occasional shock.

The authors now recommend the use of approximately 15 mc of yttrium 90 distributed in 8 or more small seeds in order to obtain complete destruction of the pituitary gland with placement of the seeds at least 3 mm. below the diaphragm of the sella and 2 mm. above its floor to prevent complications. The procedure is a useful one to obtain complete hypopituitarism in breast cancer.—Luther W. Brady, MD

McCullagh, E. Perry, Feldstein, Marvin A., Tweed, Devina C., and Dohn, Donald F. A study of pituitary function after intrasellar implantation of 90 yttrium. J. Clin. Endocrinol. & Metabol., June, 1965, 25, 832-842. (From: Department of Endocrinology, Department of Clinical Pathology, and Department of Neurologic Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio.)

The authors present an evaluation of residual pituitary function in a group of 33 patients who were originally treated with the intrasellar implantation of yttrium 90. Yttrium 90, a pure beta emitter, contained in nylon cylinders and secured in stainless steel screws, was placed within the sella turcica by a transnasal approach with the aid of an image amplifier and stereotactic apparatus. Twenty-nine of the patients had metastatic breast cancer; 2 had acromegaly; and 2 had Cushing's syndrome. The major complications encountered were a mild degree of diabetes insipidus present in all patients; cerebrospinal fluid rhinorrhea in 13 of a total of 90 patients in whom the procedure was performed; mild extraocular palsies in 4 patients; and small sector visual field defects in 2 patients.

Base line endocrine studies consisting of the determination of protein bound iodine, basal metabolic rate, 24 hr. urinary 17-ketosteroids, 24 hr. urinary 17-hydroxycorticoids and gonadotropics were performed in all cases. Six weeks after implantation of the Y90, all endocrine studies were repeated. The patients were also subjected to pituitary stimulation by metopirone. Based on the urinary excretion of 17-hydroxycorticoids in response to metopirone stimulation, 21 of the 29 patients with metastatic breast cancer were found to have severe hypopituitarism; and most had subjective and/or objective benefit from the operation. The remaining 8 had residual pituitary function and failed to exhibit any objective remission in the progression of the cancer. Dramatic subjective and objective improvement occurred in all patients with acromegaly and Cushing's syndrome following therapy.

The authors conclude that the urinary gonadotropin titer appeared to be the most sensitive measure of pituitary destruction in this series of cases.— Kenneth M. Nowicki, M.D.

Wolf, R., and Fischer, J. Erfahrungen mit der Color-Szintigraphie. (Experience with color scintigraphy.) Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin, Dec., 1964, 101, 644-652. (Address: Dr. R. Wolf, Inst. für Klinische Strahlenkunde, I. Med. Klinik und Poliklinik der Universität, Langenbeckstrasse-1, 6500 Mainz, Germany.)

With a series of color reproductions of scintigrams, the authors illustrate their conviction that color scintigraphy is preferable to black-and-white scintigraphy because it materially improves contrast without the risk of losing any information on the scan. Further, to get the same amount of information recorded on a black-and-white scan would require the expenditure of a good deal more time and an increase in the complexity of apparatus.—

Henry G. Moehring, M.D.

OZEKI, M., FURUKAWA, Y., MORIYAMA, T.,

Matsushita, H., Tsukamoto, M., and Kohi, T. The basis of multiscintigram system and its clinical applications. *Kurume M.* J., 1964, 11, 149–166. (From: Department of Radiology, Kurume University School of Medicine, Kurume, Japan.)

The multiscintigram system is apparently one in which color solenoid prints are made with certain colors assigned to various portions of the response spectrum. Thus the authors' unit will make color scintigrams much like those produced by available American systems.

The authors have adapted their printing circuit to operate additional solenoids with which each of the separate color ranges may be printed independently.

A block diagram of their circuit is supplied, and there are a number of color scan reproductions and matching roentgenograms.—Frederick J. Bonte, M.D.

CHEMOTHERAPY

Montgomery, D. A. D., and Welbourn, R. B. Adrenocortical carcinoma treated with o,p¹-DDD. *Brit. M. J.*, May 22, 1965, 1, 1356-1358. (Address: D. A. D. Montgomery, Physician-in-Charge, Sir George E. Clark Metabolic Unit, Royal Victoria Hospital, Belfast, Ireland.)

As early as 1949, the insecticide DDD was noted to cause selective necrosis of the zona fasciculata and zona reticularis of the adrenal cortex in dogs. Its use in man proved unsuccessful. However, it was discovered that a contaminant of crude DDD, the ortho-prime isomer, 0,p¹-DDD (2[2-chlorophenyl]-2-[4-chlorophenyl]-1,1-dichlorethane), was a much more effective drug. Its action in the treatment of adrenocortical cancer has subsequently been investigated.

o,p¹-DDD apparently destroys adrenocortical tissue directly, but is unpredictable. Many patients with adrenocortical tumors have shown no response. The drug is given orally in a dose of 6–10 gm. daily. Toxic reactions are common.

The authors present a case of adrenocortical carcinoma in a girl aged 3 years 4 months. The patient presented with the typical clinical findings of hyperadrenocorticism and a large mass in the left hypochondrium. No metastatic disease was noted prior to surgery. The patient did well for 4 months after the operation and then lung metastases were noted on roentgenologic examination.

Treatment with o,p¹-DDD followed 2 months after the diagnosis of pulmonary metastases. During this 2 month interval the liver became large and revealed multiple nodules. The disease in the lungs also progressed. The dose was started at 3 gm. daily and gradually increased to 8 gm. daily 4 weeks later.

Cortisone was also started at this time. The dose of the o,p¹-DDD at which objective response occurred was found to be 8 gm. daily.

There was marked regression of both the size of the liver and the pulmonary metastases. The child was doing very well at home 4 months after the o,p¹-DDD therapy was started when she died suddenly, having developed a febrile illness, possibly measles, 2 days before death.

Postmortem examination revealed viable tumor in the liver and lungs. There was, however, a great deal of necrosis in most areas of the tumor.—
Ronald Schaupp, M.D.

Kennedy, B. J. Diethylstilbestrol versus testosterone propionate therapy in advanced breast cancer. Surg., Gynec. & Obst., June, 1965, 120, 1246–1250. (From: Department of Internal Medicine, University of Minnesota Medical Center, Minneapolis, Minn.)

A comparative randomized study of the effectiveness of diethylstilbestrol and testosterone propionate in the treatment of metastatic breast malignancy in postmenopausal women was conducted by the author. Some 59 women whose menopausal ages varied from 1 year after castration to more than 10 years postmenopausal received testosterone; 55 women in the same age group received diethylstilbestrol.

Objective evidence of tumor regression was achieved in 29.1 per cent of the cases treated with diethylstilbestrol as compared to 10.1 per cent treated with testosterone propionate. The median duration of remission was 11+ months and 9.7 months for the 2 respective groups. The duration of survival, however, was found to be greater for those patients who showed a positive response to either hormonal agent. Objective responses occurred primarily in the older postmenopausal groups and were seldom found in patients less than 5 years postmenopausal.—Donald S. Faust, M.D.

Hammack, William J. Chemotherapy of metastatic malignancy. GP, June, 1965, 31, 120–130. (From: Division of Hematology, Department of Medicine, Medical College of Alabama, Birmingham, Ala.)

A general discussion and classification of the 4 main groups of chemotherapeutic agents are presented.

Specific information on each individual drug such as formula, mode of action, and usage in disease states is included. Finally, specific disease entities are considered individually with the drugs of choice listed in order of the author's preference. A discussion of the average dosage and its administration, together with side effects and drug toxicity are given for each agent.

In all, 12 specific disease entities are considered separately.—Donald S. Faust, M.D.

MISCELLANEOUS

Ogawa, Elichi, Suzuki, Shiro, Fujii, Shunichi, Honma, Tsuyoshi, and Tsuzuki, Hiroshi. Studies on the elimination of radioactive strontium: effects of the administration of various compounds. Gunma J. M. Sc., Sept., 1964, 13, 214–220. (From: Department of Pharmacology, School of Medicine, Gunma University, Maebashi, and Maebashi Laboratory, Institute of Radioisotopes, Gunma University, Maebashi, Japan.)

This is a report on the efficacy of various chemical and hormonal agents on the elimination of radio-active strontium previously administered to mice. Carrier-free Sr⁸⁶ or Sr⁹⁰ nitrate was administered subcutaneously to the various groups of mice. Immediately after the isotope administration one of several drugs was given by intraperitoneal, subcutaneous, or intramuscular routes. Subsequent administration of the drug was made on a daily basis for 2 days. Examination was made of the excretion of the radioactive material in the urine and feces and also that which was retained in the skeleton.

Of the chelating agents used, Na Sr citrate and aspartic Mg K in combination with NH₄Cl displayed some effect on the elimination of Sr²⁶. Sodium ATP and tetracycline increased only the excretion of the radioactive material without diminishing the retention in bone. BADE, either alone or in combination with strontium chloride was not effective.

Sodium thiosulfate alone or in combination with strontium chloride was the only salt which appeared effective in eliminating some of the radioactive strontium. Other preparations including calcium gluconate, sodium polyphosphate and chondroitin sulfuric acid exerted no effect.

None of the diuretics including diuretin, caffeine sodium benzoate, sodium thiocyanate, mannital and chlorothiazide showed any effect on the elimination of radioactive strontium.

Several hormones, vitamins and metabolic inhibitors were tested. Of these, the glucocorticoids appeared to have the greatest effect on the excretion of strontium and, therefore, decreased retention of strontium in the skeleton. Likewise TSH and cocarboxylase were shown to be somewhat effective. Antithyroid drugs, on the other hand, appeared to decrease the normal elimination of radioactive strontium. NaF appeared to increase the bone deposition of radioactive strontium.

Although no conclusions are drawn from this study, it is apparent that none of the rather large group of drugs employed appear to provide a practical method for elimination of previously

administered radioactive strontium.—Merle Loken, M.D.

MARTINEZ, G. R., CASSAB, H. G., GANEM, G. G., GUTTMAN, K. E., LIEBERMAN, L. M., LINARES, M. M., RODRIGUEZ, M. H., and VATER, B. L. Observaciones sobre la exposición accidental de una familia a una fuente de cobalto 60. (Observations on the accidental exposure of a family to a cobalt 60 source.*) Rev. méd. d. Instit. Méx. d. Seguro Social, 1964, 3, 1–68. Suppl. No. 1.

This is a report of a radiation accident that occurred in 1962 in Mexico City. It involved 5 members of a family, 4 of whom died due to total body irradiation.

The accident was bizarre, and so unexpected that the true nature of the disease was not suspected until after 2 of the victims had already died, and was not finally clarified until 1 more member of the family had also died.

Some particulars about the accident have not been completely understood up to this time, and the radiation doses received by the victims have been only roughly estimated.

The accident occurred in the following manner: On March 21, 1962, a family consisting of husband, wife, a 10 year old son, and a younger sister moved into a house. In this house there was a lead container, that had been left there for the family to keep and watch. The container held a 5 curie source of cobalt 60 of the type used for industrial radiography, but this was not known by any of the members of the family.

Sometime between March 21, the day the family moved into the house, and April 1, the capsule was taken out of the container. During this time interval the boy found the capsule in the yard, and kept it in the left pocket of his trousers. On April 1, his mother took the capsule from the boy's trousers and put it in the drawer of a kitchen table, where it remained until July 22, when it was removed by its owner.

On April 17, about 1 month after the family moved into the house, several of its members became ill, and the husband's mother came to live with them to take care of them. The grandmother eventually died, as did the mother, son and daughter. Only the husband has survived.

The nature of the disease was first suspected in August by a doctor who saw the sick grandmother in an out-patient clinic. By the time the puzzle had been put together, the capsule was no longer in the house, and it was necessary to do a great deal of reconstruction of the circumstances of the accident to arrive at a reasonable estimate of the magnitude of

* A review of this article was presented by Dr. Comas at the Forty-seventh Annual Meeting of the American Racium Society, New Orleans, Louisiana, April 8-10, 1965.

the doses received. The calculations were, by necessity, only approximate, and after much work had been done, it was decided to accept a minimum and a maximum exposure dose for each member of the family.

It was estimated that the boy had received from 2,940 to 5,165 rems, in a time interval of 24 days, of total body irradiation. In addition he received several tens of thousand rads to the left thigh. He first developed erythema in the left thigh, which extended to the lower abdomen and scrotum. This rapidly progressed to a deep and extensive necrosis which was taken to be an abscess. One day after the appearance of the erythema he manifested anorexia, vomiting, fever, diarrhea, and I week later weakness and listlessness. He was admitted to a hospital where he died, after 12 days, with semicoma, Cheyne-Stokes respiration, high fever, bloody diarrhea, and intermittent contractions of the upper extremities.

Next to die was the mother. It is estimated that her total body dose was between 1,995 and 2,938 rems in 115 days of exposure. During the first week of exposure she showed anorexia, nausea and vomiting. These symptoms were attributed to her pregnancy. She was 2 months pregnant at that time. On the third week of exposure she developed low grade fever, night sweats, and blackening of the fingernails. Starting on the fourth week she developed intermittent hemorrhages, petechiae, leukopenia and thrombocytopenia. Autopsy showed bone marrow aplasia. The fetus showed no malformations, and indeed no major abnormalities other than depletion of the lymphoid tissues and absence of hemopoiesis in the spleen and lymph nodes.

The girl received between 1,372 and 1,872 rems in 99 days of exposure. Her course was similar to that of her mother. She died 146 days after the beginning of exposure. At autopsy there was bone marrow aplasia. The immediate cause of death was massive hemorrhage in the adrenal glands and associated

with hemorrhage in the gastrointestinal tract.

The grandmother received between 897 and 1,818 rems in 90 days. Two weeks after beginning of exposure she showed general weakness and blackening of the nails. She did not consider herself sick, however, until after 70 days of exposure. By then she had hemorrhagic manifestations consisting of epistaxis, bleeding from the gums and bloody sputum. At that time her hemoglobin was 4.9 gm. per cent, and she had 2,000 white blood cells per ml. The true diagnosis was made at this point, but all therapeutic measures were to no avail, and she died 3 months later. At autopsy there was bone marrow aplasia and massive pulmonary hemorrhage.

The husband received the least exposure because he was out at work most of the day. He received between 984 and 1,716 rems in 119 days. He also showed blackening of the nails and symptoms attributable to bone marrow depression. He has, however, recovered completely as far as can be ascertained.

This accident is unique in that the exposure took place over many days. This makes it different from all other reported radiation accidents which have been the result of short, intense exposures.

It seems that the boy died as a result of central nervous system and intestinal injuries. All others exhibited the bone marrow depletion syndrome in a more or less acute form, depending on the amount of radiation accumulated. Mother, daughter and grandmother showed no signs of bone marrow regeneration, although they lived from a few weeks to 3 months after exposure had ceased.

Taking into account that the grandmother received a maximum dose of 1,818 rems in 90 days and died, and that the father received a maximum dose of 1,716 rems in 119 days, and survived, one might speculate that a dose intermediate between the two may be fatal when received in a time interval of 3 to 4 months.—F. V. Comas, M.D.



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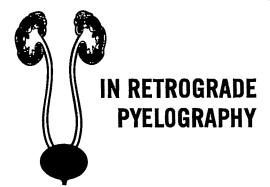
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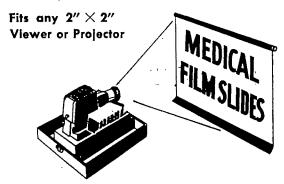


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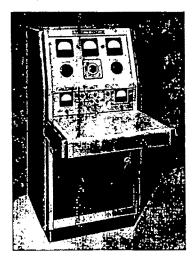
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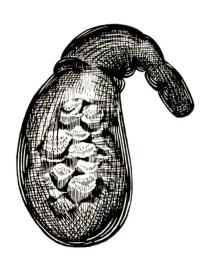
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IN ORAL CHOLANGIOGRAPHY AND CHOLECYSTOGRAPHY



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Supply: Oragrafin Calcium Granules—single-dose foil packets of 3 Gm. of calcium ipodate granules, providing 61.7% iodine content. Oragrafin Sodium Capsules—0.5 Gm. sodium ipodate per capsule, providing 61.4% iodine content.

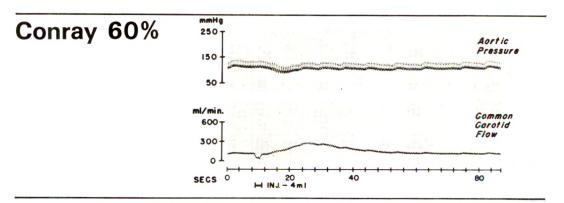
Side Effects: Nausea, vomiting, diarrhea, headache, dysuria, and abdominal pains occur infrequently. Hypersensitivity reactions may include urticaria, serum sickness-like reactions, skin rashes, and rarely anaphylactoid shock.

Precautions: Contraindicated for persons sensitive to oral iodine compounds or for patients with combined renal and hepatic disease or severe kidney impairment. Gastrointestinal disorders (which may result in inadequate biliary secretion of medium) often impair visualization. For full information, see Product Brief.

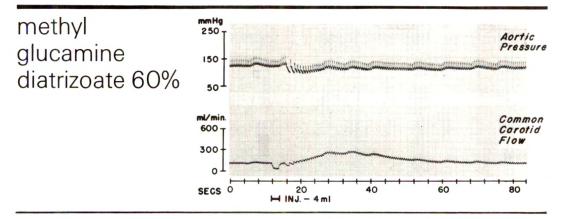


The Compatible Contrast Agent

Conray[®] (Meglumine lothalamate 60% Injection U.S.P.)

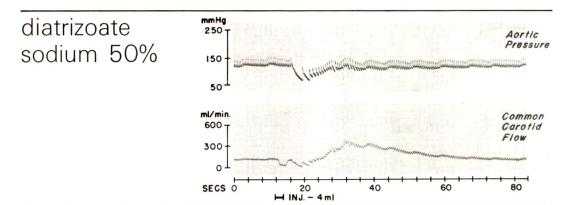


Recent experimental studies* of the comparative toxicity of various contrast agents reveal Conray is more compatible physiologically than other agents. Following injections into the common carotid artery of dogs, Conray produced the least hemodynamic change.



In this graph, greater hemodynamic disturbances are seen following the injection.*

least irritation at injection site least hypotensive effect least systemic stress



This graph shows marked hypotension following the injection of the medium. Note that the common carotid blood flow reaches the zero level for a few seconds. "This decrease in the carotid flow undoubtedly plays an important role in the production of neurological complications."*

Sequential injections were made into the internal carotid artery to determine "The Least Convulsive Dose" of the three media. The following results were obtained:

Meglumine iothalamate 60% (Conray)	25 ml.
Meglumine diatrizoate 60%	16-20 ml.
Sodium diatrizoate 50%	10-12 ml.

Based on the results of the complete study, the investigator concluded, "Of all the currently available contrast agents tested, Meglumine lothalamate produces the least hemodynamic changes and exerts the least convulsive effect."*

^{*}Hilal, S. (Department of Radiology, Neurological Institute, Columbia-Presbyterian Medical Center, New York): Paper presented VII International Symposium Neuroradiologicum, New York, Sept., 1964.

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(Sodium Iothalamate Injection U.S.P. 66.8%)

for intravenous urography, intravascular angiocardiography and aortography

Product Particulars

CONRAY: Each ml. contains 0.6 Gm. meglumine iothalamate; not more than 0.11 mg. calcium disodium ethylenediaminetetraacetate as stabilizer; not more than 0.15 mg. sodium biphosphate as a buffer.

Angio-CONRAY: Each ml. contains 0.8 Gm. sodium iothalamate; not more than 0.135 mg. calcium disodium ethylenediaminetetraacetate as stabilizer; not more than 0.15 mg. sodium biphosphate as a buffer.

CONRAY-400: Each ml. contains 0.668 Gm. sodium iothalamate; not more than 0.135 mg. calcium disodium ethylenediaminetetraacetate as stabilizer; not more than 0.15 mg. sodium biphosphate as a buffer.

Side Effects: With CONRAY (meglumine iothalamate 60%) these have been minor and infrequent, and include nausea, vomiting, urticaria, However, as with any iodinated intravascular conrast agent, the possibility of severe reactions exists (neurological complications, the so-called anaphylactic response and cardiovascular collapse). With Angio-CONRAY (sodium iothalamate 80%) and CONRAY-400 (sodium iothalamate 66.8%) rapid injection has produced a wave of warmth or heat passing over the body, often associated with flush. Other transient reactions infrequently observed are nausea, vomiting and bitter taste. In rare instances, injection of a con-

trast medium has been reported to produce more serious reactions including fatalities. *Note:* Because of the possibility of severe reactions to any medium, patients should not be left alone for at least 15 minutes following injection.

Caution: CONRAY-400 (sodium iothalamate 66.8%) and Angio-CONRAY (sodium iothalamate 80%) are not intended for use in cerebral angiography. For this purpose, CONRAY (meglumine iothalamate 60%) is recommended.

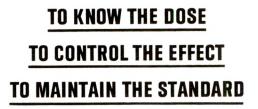
Contraindications: For all three media, caution is required in cases involving severe systemic disease. In patients with advanced renal disease, use with caution and then only when need for examination dictates. In patients with a history of allergy or those exhibiting a positive reaction to the sensitivity test, drugs and facilities for emergency use must be readily available.

Precautions: For Angio-CONRAY (sodium iothalamate 80%) and CONRAY-400 (sodium iothalamate 66.8%), cardiac arrhythmias, including ventricular fibrillation, have been reported with the use of these media in procedures for visualizing the heart and its associated large vessels. Such occurrences may be associated with situations in which appreciable amounts of relatively undiluted medium enter the coronary circulation. Facilities for immediate treatment of such reactions should be available.





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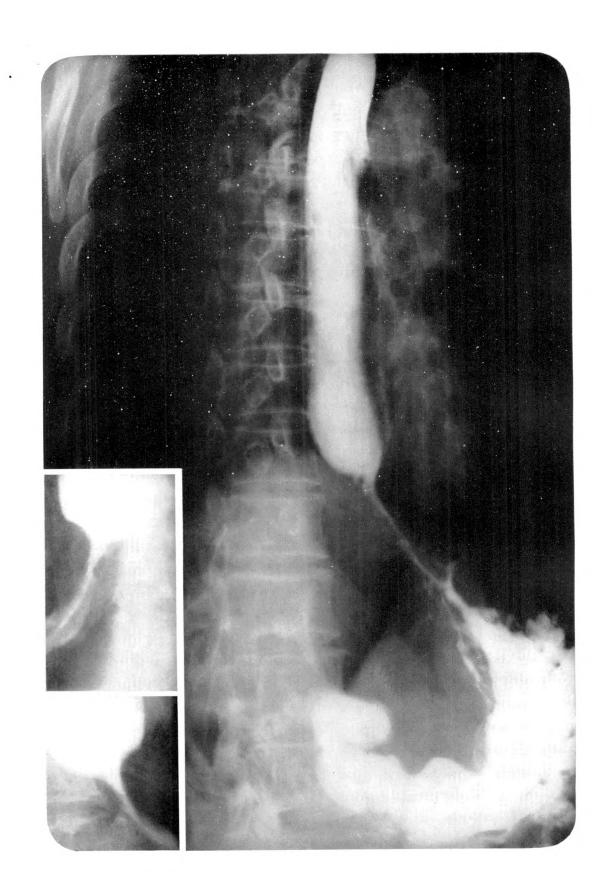
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Esophagograms revealed obstruction and delay in the lower third of the esophagus two inches above the diaphragm. Borders of the esophagus were smooth. However, the abrupt change in contour and the shelf formation seemed to rule out cardiospasm. The findings had the appearance of carcinoma.

Esophagoscopy with biopsy confirmed the radiologist's findings. The pathological diagnosis was squamous cell carcinoma of the esophagus.

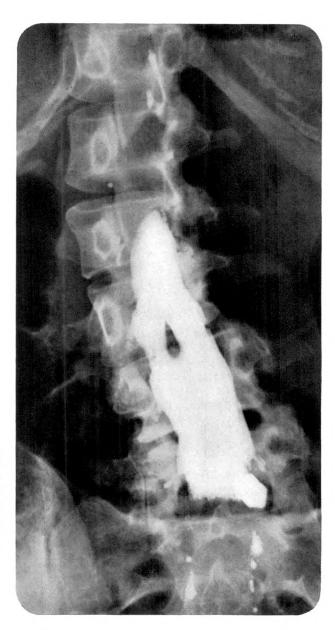
GAF High Speed X-ray Film was used to reveal the cause of the man's dysphagia. This film provides the high contrast and fine definition necessary for radiographic studies demanding the ultimate in diagnosis. The high contrast was particularly helpful in diagnosing this patient's carcinoma.

Following the administration of barium, a radiograph on GAF High Speed X-ray Film showed an obstruction of the lower third of the esophagus with a shelf formation.



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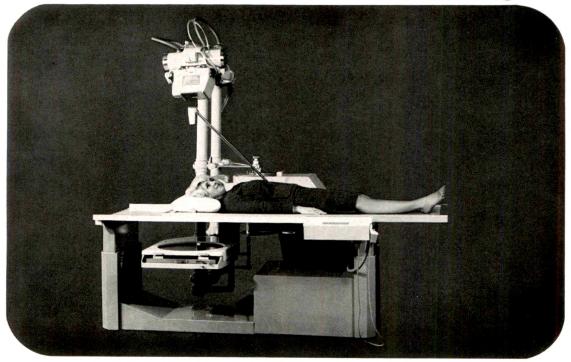
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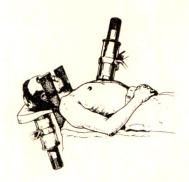
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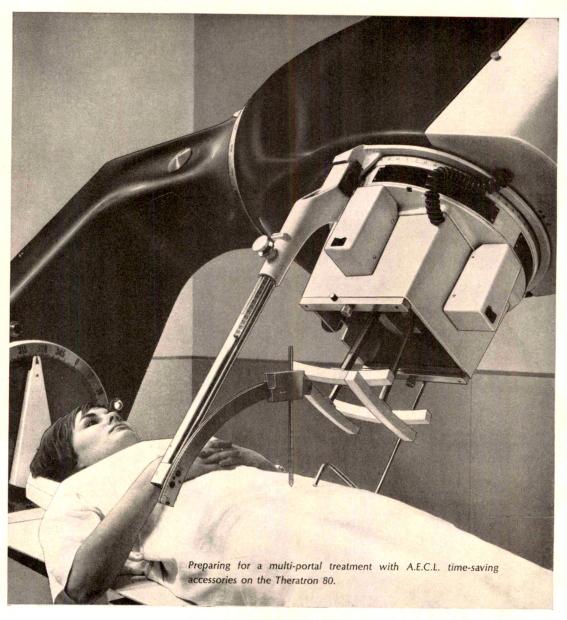
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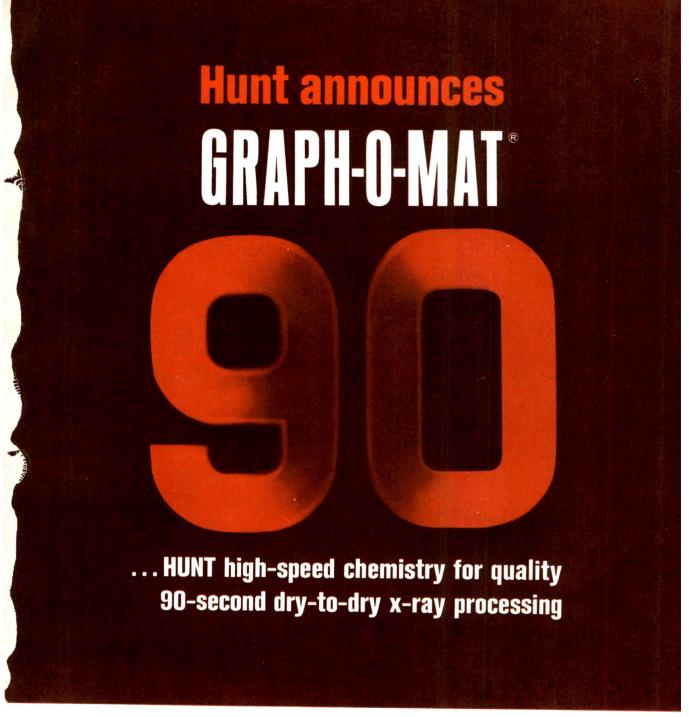
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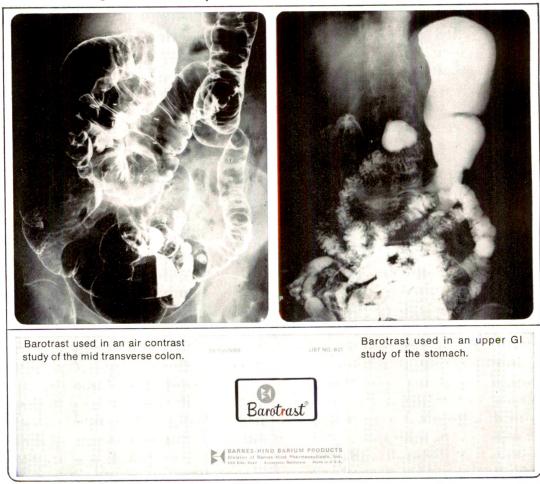
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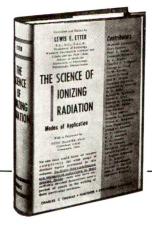
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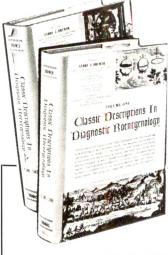


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Modes of Application

compiled and edited by Lewis E. Etter, Univ. of Pittsburgh, Pittsburgh, Pa. (With 35 Contributors) Foreword by Otto Glasser. No one man could master completely the wide range of distinct topics presented in this volume. Its thirty-five contributors are recognized authorities in their specific fields-men who have devoted themselves over a period of years to the writing of their particular sections. The result is a remarkable presentation of the science including history, equipment, radiation physics, recording media and screens, chemistry, radiobiology, human application of ionizing radiation, applications in industry, crystallography, paleontologic-archaeologic applications, anthropological applications, radiography of graphic art, application in agriculture, and protection. Will acquaint the individual scientist with the latest changes in his specialtyas well as related specialties.

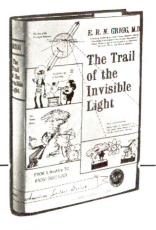
1965 804 pp. (6¾ × 9¾) \$26.50 483 il., 29 tables



CLASSIC DESCRIPTIONS IN DIAGNOSTIC ROENTGENOLOGY

edited by André J. Bruwer, Tuc-son Medical Genter, Tucson, Ariz. (With 35 Contributors) Seven years of meticulous labor have gone into the compiling and editing of this historic work. Its purpose is primarily idealistic-a token of recognition and respect for those scientists and physicians in many countries who developed the techniques on which modern diagnostic roentgenology is based. These pioneer works are-in most cases reproduced in their complete form—in many instances translated from the original. It is impossible to describe even briefly the contents of so comprehen-sive a work. There are chapters on angiocardiography and thoracic aortography, phlebography, fluoroscopes and fluoroscopy, cineroentgenology, myelography, etc. There are pioneer descriptions in obstetrical and gynecological roentgenology, military roentgenology, and veterinary roentgenology, and Superbly illusroentgenology. trated throughout. In Two Vol-

1964 2,094 pp. (7 × 10) \$49.50 1,727 il.



THE TRAIL OF THE INVISIBLE LIGHT From X-Strahlen to Radio(bio)logy

by E. R. N. Grigg, Cook County Hosp., Chicago, Ill. Here is the fascinating story of the first clinical roentgen plate including sidelines which add a human touch. Here also is the story of American X-Ray makes and makers-beginning with the very first year, 1896. In a radiosemantic treatise the author begins with a listing of the numerous roots proposed and actually used to indicate x-rays. He then covers the three stages in the history of radiology . . The Era of the Roentogen Pioneers, The Golden Age of Radiology, and The Atomic Phase. Four other "firsts" to be found in this volume are a list of all significant radiologic periodicals, a radio-historic bibliography, a world-wide almanac of x-ray manufacturers, and an abbreviated dictionary of radiologic biography. (Amer. Lec. Roentgen Diagnosis edited by Lewis E. Etter)

1,016 pp. (8½ × 11) \$36.75 About 1,404 figs.

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- □ CASE OF THE DAY by Benjamin Felson and Jerome F. Wiot, both of Univ. of Cincinnati. Mar. '66, about 128 pp. (6¾ × 9¾), about 100 il., (Amer. Lec. Roentgen Diagnosis edited by Lewis E. Etter). In Press
- ☐ THE EARLY RADIOLOGICAL DIAGNOSIS OF DISEASES OF THE PANCREAS
 AND AMPULLA OF VATER: Elective
 Exploration of the Ampulla of Vater and
 the Head of the Pancreas by Hypotonic
 Duodenography by Paul Jacquemet, Lyon
 Faculty of Medicine, Lyon, France; Domingo Liotta, Baylor Univ., Houston; and
- Pierre Mallet-Guy, Lyon Faculty of Medicine. Translated by Lee D. Cady, Baylor Univ. '65, 256 pp. (7×10) , 392 il., \$14.50
- ☐ SURGICAL APPLICATIONS OF LASER by Paul Edward McGuff, Laser Medical Research Foundation, Boston. Jan. '66, about 224 pp., about 70 il., 56 tables. In Press
- □ CLINICAL ROENTGENOLOGY OF COL-LAGEN DISEASES by Charles M. Nice, Jr., Tulane Univ. Jan. '66, 216 pp., 134 il., (Amer. Lec. Roentgen Diagnosis), \$10.75

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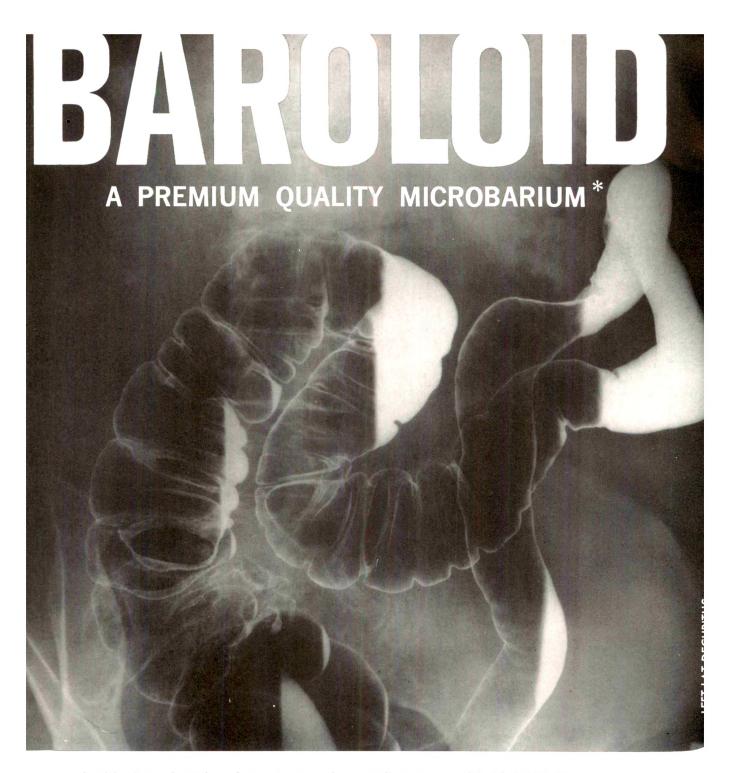
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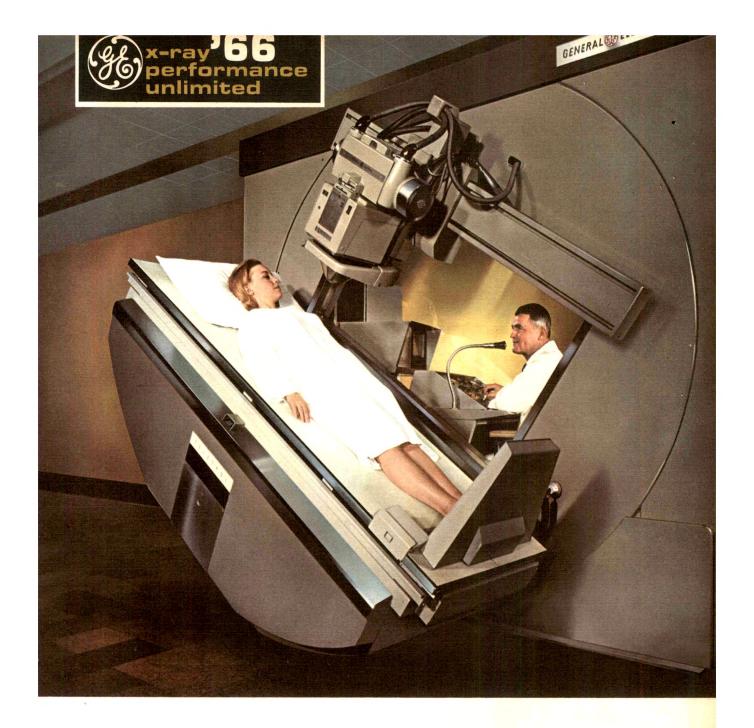
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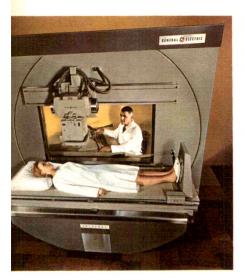
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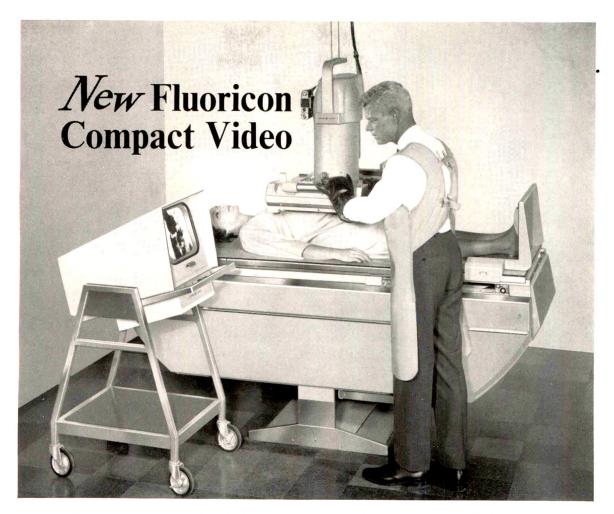
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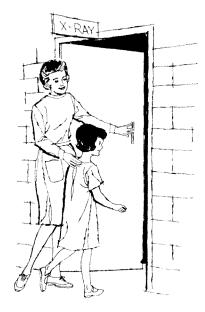
Neuroendocrinology has gained recognition as a field of research in its own right only in recent years, but it is a rapidly expanding field which promises a bright future. Articles on neuroendocrine subjects have up to now been spread over a wide variety of journals, and it is hoped that this new journal, which will publish original and brief review papers on experimental and clinical studies on neuroendocrine relationships, will serve to keep clinicians and research workers informed on latest developments in this field without the task of searching for relevant articles through many publications on other topics. Indeed, this very diversity of interests, techniques and subject matter in the field of neuroendocrinology is precisely the reason for the need of an organ in which the many threads can be gathered to be woven into a patterned matrix.

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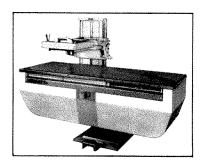
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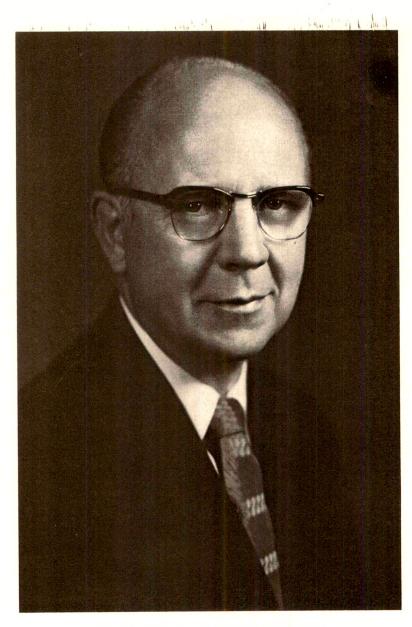
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CLYDE A. STEVENSON Caldwell Lecturer, 1965

THE AMERICAN JOURNAL OF ROENTGENOLOGY

RADIUM THERAPY AND NUCLEAR MEDICINE

Vol. 96

FEBRUARY, 1966

No. 2

INTRODUCTION OF CALDWELL LECTURER

By C. ALLEN GOOD, M.D. ROCHESTER, MINNESOTA

The man who will address us tonight is an old and valued friend of mine. A little more than 30 years ago, we began training in radiology at the same institution. As we shared experiences and grew in wisdom—at least I like to think we did—we developed a friendship that has lasted all of these years, in spite of the fact that we have lived in different parts of the country.

The capacity for strong friendship is one of our speaker's great assets, and he has many. There are others in this audience tonight who know him as a true friend and who trust him and admire him as I do. We all benefit from his willingness to give of himself in order to do something for us. He does this, and has done it for so many years, that we are inclined to take it for granted. Tonight, in honoring him as the Caldwell Lecturer, we are perhaps repaying him a little for his years of service to us all.

Clyde Alan Stevenson was born in Milwaukee about the time that Eugene Caldwell was elected President of the American Roentgen Ray Society. He was educated at the University of Wisconsin where he made an enviable record, both as an undergraduate and as a medical student. The key of Alpha Omega Alpha that he wears attests his scholarship.

Following an internship at St. Luke's Hospital in Duluth, Minnesota, he began a Fellowship in Radiology at the Mayo Clinic and Mayo Foundation. He left to help Lester Baird reorganize the Department of Radiology at Scott and White Clinic, Temple, Texas. After Dr. Baird's untimely death, he became head of the department and was responsible for the training of many excellent radiologists.

Before he left Scott and White Clinic in 1955, he had served as Professor of Radiology at University of Texas Post-Graduate Medical School; Lecturer in Radiology at the Medical School of the University of Texas in Galveston; and Consultant in Radiology to the Veteran's Administration Hospital, Temple, Texas, to the National Institutes of Health, Bethesda, Maryland, and to Fort Hood Station Hospital, Fort Hood, Texas.

During his sojourn in Texas he continued to develop his great capacity for friendship and service to others, and became a member of the five-man Board of Directors of Scott and White Clinic, and a trustee of Scott and White Memorial Hospital. Dr. Stevenson became President of Bell County Medical Society and President of Texas Radiological Society.

It was during this period, too, that he began serving the members of the American Roentgen Ray Society as a member of its Executive Council, ultimately becoming Chairman in 1953. Eight years later our Society honored him by electing him to the office of First Vice-President.

Such opportunities for service would keep an ordinary man completely occupied, but our speaker also found time for scholarly endeavors. He was the first to describe in this country the changes in bone resulting from ingestion of fluorides. As a result he became a member of a team of workers from the United States Public Health Service which labored for 10 years to establish the medically safe dosage of fluoride for the prevention of dental caries. He still works on this problem in conjunction with the Kettering Laboratory of the University of Cincinnati.

He carried out research on the roentgenologic examination of the colon that culminated in an exhibit that won the Gold Medal at the meeting of the American Medical Association in 1949. In 1953, he delivered the Hickey Memorial Lecture in Detroit on the subject "The Development of the Colon Examination." His bibliography includes about 35 published papers and a chapter in a Spanish language book on gastroenterology.

In 1955, Dr. Stevenson left Texas for Spokane, Washington, to become Director of the Department of Radiology of Sacred Heart Hospital, a post he still holds. Here he continues his service to Radiology by training residents, by acting as Consultant in Radiology to several state and federal hospitals, by serving as Secretary of the Section on Radiology of the American Medical Association and as a trustee and regular examiner of the American Board of Radiology.

It is entirely fitting, therefore, after 30 years of service to radiology and medicine, of scholarship, and above all of true friendship, that President Medelman should select Clyde Stevenson to deliver the Caldwell Lecture tonight.

Ladies and Gentlemen, I am proud to have the honor of presenting to you my great friend, Clyde A. Stevenson, the Caldwell Lecturer of 1965. He will speak to you on the subject "Clinical Roentgenology of the Colon."

The Mayo Clinic Rochester, Minnesota



CLINICAL ROENTGENOLOGY OF THE COLON*

CALDWELL LECTURE, 1965

By CLYDE A. STEVENSON, M.D.†

SPOKANE, WASHINGTON

BY CHOOSING the title "Clinical Roentgenology of the Colon," I hope to emphasize that this examination is not a perfunctory procedure, but actually is a complicated method of indirect physical examination of a patient by a physician. In choosing roentgenologic equipment and procedures to aid him in detecting the presence or absence of disease in the colon, the physician implies a special ability to transpose a visualized black, grav and white image into a mental picture of living tissue in full color and three dimensions. From that point on, the worth of the examination is dependent not only upon the roentgenologist's knowledge of pathology, but upon his ability to view his findings from the standpoint of a well-informed clinician or surgeon.

My long continued interest in clinical roentgenology of the colon began more or less automatically when I was a student under Drs. Harry M. Weber, A. C. Broders, W. C. McCarthy and J. A. Bargen. Dr. Weber, the 54th President of the American Roentgen Ray Society and a long time Director of our annual meeting Instruction Courses, began intensive work on the colon examination in 1930 and his monumental achievements form the solid framework for our present concept of colon diseases. Drs. Broders and McCarthy were outstanding pathologists in the area of gastrointestinal disease while Dr. Bargen wrote his name indelibly across the pages of gastrointestinal literature and became nationally and internationally acclaimed for his knowledge and contributions concerning the medical aspects of colon disease.

It seems fitting that our present assembly in honor of Dr. Caldwell should also be an

appropriate occasion to pause, pay respect and recognize our continuing intellectual debt, not only to those recalled by name, but to the many others, who, by word or deed, have guided us to our present knowledge of clinical roentgenology of the colon.

A better understanding of the present status of the colon examination may be gained by a brief review of historic highlights. During the first 10 years of this century, investigators in Europe and in this country devised various methods of obtaining a roentgen image of the colon. During the next 10 years, Brown and Sampson, Case, Cole and Carman¹⁷ were able to show roentgen evidence of colon disease and by 1920 tuberculosis of the terminal ileum, diverticulosis and diverticulitis, chronic ulcerative colitis, carcinoma, polyposis and megacolon could be recognized. From 1920 to 1930, the roentgenologic examination of the colon became an established and wellaccepted procedure with Hickey making significant contributions and Fischer of Germany describing his double contrast method for detection of intraluminal neoplasms. In 1930, Weber began reporting his experiences with the colon examination. He gave intensive study to the work of his predecessors, improved on Fischer's technique and devoted practically all of his time and effort to clinical roentgenology of the colon in many thousands of patients. By consultation and study with his associates in proctology, gastroenterology, surgery and pathology, he was able to formulate accurate roentgen criteria for the diagnosis of various colon diseases and his written descriptions remain classic. Weber's untimely death in 1958 closed a most im-

^{*} Presented at the Sixty-sixth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., September 28-October 1, 1965.

[†] Director, Department of Radiology, Sacred Heart Hospital, Spokane, Washington.

portant era in the development of the colon examination.

In recent years many investigators have emphasized refinements in method and technique, but the examination remains difficult and is often done under circumstances not conducive of maximum benefit to the patient. Just as with any diagnostic or therapeutic procedure in the practice of medicine, the colon examination reaches a high state of perfection in the hands of a well-trained and experienced roentgenologist with an intense interest in the field and especially when he is associated with equally qualified and enthusiastic specialists in related fields. The nation-wide status of the examination is not uniformly high, the problems are many and varied and the near future holds no promise of major change in diagnostic methods. However, knowledge is not lacking for improved performance and a discussion of major problems and limitations can lead to better health care for our people. For the purposes of this discussion, these problems will be classified as extrinsic or intrinsic with extrinsic being those not directly controlled by the roentgenologist and intrinsic referring to those of iatrogenic origin.

The extrinsic problems are generated mainly by lack of communication with the patient's physician and the need for him to understand that if he wants his patient to obtain maximum benefit, certain pre-examination requirements must be fulfilled. Lack of clinical correlation, omission of the proctosigmoidoscopic examination and inadequate preparation of the patient cause many roentgenologists to feel handicapped and frustrated in their effort to give the patient full benefit of their services as consultants.

CLINICAL CORRELATION

Probably the most common complaint is that a request for a colon examination is seldom accompanied by significant information from the patient's physician. From the day of the pioneer up to the present time, all who have made significant contributions to the development of the colon examination have emphasized the necessity of close and complete cooperation between the clinician, surgeon, roentgenologist and pathologist. Hickey⁹ stated, "The roentgenologist is a practicing physician and should be, and usually is, well educated in clinical history, modern pathology and correlated methods of diagnosis. If he acquaints himself with the clinical symptoms, he will be able to stress certain parts of his examination productive of value to the clinician and patient." The roentgenologist of today, faced with his increasing burden of work, seldom finds the time to follow Hickey's advice, but is usually dependent upon the patient's physician for significant facts from the history or physical examination. In speaking of the accuracy of the roentgenologic examination of the intestinal tract, Sosman¹² said, "The highest accuracy and greatest benefit to the patient accrue when the physician, surgeon, or gastroenterologist work closely with the roentgenologist sharing their facts, ideas and suspicions as well as their experience and judgement."

Today, roentgenologists continue to recognize the need for significant clinical information. This sets up a diagnostic goal, helps in selection of the appropriate type of examination and, at times, serves as a warning flag that the examination should be avoided, postponed or replaced by some other diagnostic test.

In modern times the patient's physician often obtains a history of a previous colon examination and then all effort should be made to obtain the report and roentgenograms for review and study before the current examination is done. The report alone should not be considered adequate and one may have to explain that, in addition to human error, roentgen interpretation is subject to considerable variation from one examiner to another.

ENDOSCOPY

Roentgenologists are in full accord that, as far as the patient is concerned, the proc-

tosigmoidoscopic examination is the single most important procedure in the examination of the colon. From a roentgenologic viewpoint, the endoscopic findings often indicate the roentgen method to be employed and may warn of potential traumatic complications in the distal bowel. A further benefit is the determination of the approximate area where direct vision stops and roentgenologic responsibility begins. At the conclusion of his examination, the roentgenologist often finds that he can make a more accurate clinical diagnosis if he has knowledge of the endoscopic findings. These statements clearly indicate that for maximum benefit the endoscopic findings must be reported to the roentgenologist before he begins his examination.

While roentgenologists may complain of the omission of the proctosigmoidoscopic examination, they realize that the patient has the most right to complain. As physicians, we know that just about 70 per cent of all disease affecting the colon can be detected by endoscopy and it seems illogical to limit the investigation to the other 30 per cent. Of course, these facts are generally appreciated and we can only hope for intensification of efforts to promote a more general acceptance of the procedure.

PREPARATION

The third extrinsic factor commonly affecting the colon examination is inadequate preparation of the patient. Commonly accepted routine methods of cleansing of the bowel usually prepare the area for adequate roentgenologic study, but the patient's physician is easily influenced to advise restricted efforts. Severe diarrhea, bleeding or suspected obstruction obviate any routine and call for individual variation. Routine methods often are not adequate in the elderly, nonambulatory or chronically debilitated patient and variations from routine should be considered if the examination is to show the presence or absence of any minimal pathologic process. A superior method, if medically and economically feasible, is the use of a liquid, low-residue diet for 2 or 3 days followed by castor oil or other nonhydragogue cathartic. All physicians interested in the colon examination should be aware that cleansing of the living colon cannot approach the effectiveness of mechanical washing as done by the pathologist.

The history and physical examination should play an important role in determining the scheme of preparation, but considerable additional help may be obtained by estimation of bowel content as noted on a pre-examination scout roentgenogram of the abdomen.

For those roentgenologists adversely affected by these three extrinsic factors, I would suggest that they prepare a "white paper," post it in their office, clinic or hospital and let it read as follows:

"If my doctor wanted me to have a colon examination, I would—"

- 1. Have a proctosigmoidoscopic examination.
- 2. Have this report and any significant facts from my history or physical examination sent to the roentgenologist.
- 3. Have any previous colon roentgenograms sent to the roentgenologist.
- 4. Have a scout roentgenogram made of my abdomen 2 or 3 days before the colon examination.
- 5. Have the type of preparation determined by consultation between my clinician and roentgenologist.
- 6. Have a joint consultation between my physician and roentgenologist concerning the final diagnosis.

This individual effort must be enlarged by appropriate presentations at nonradiologic medical meetings and by publications in medical literature other than our own.

INTRINSIC PROBLEMS

Like the extrinsic problems, the intrinsic problems confronting the roentgenologist in his examination of the colon are many and varied. Some of the most interesting and challenging ones occur when dealing with (1) diverticular, (2) ulcerative or (3) neoplastic disease in the adult.

1. DIVERTICULAR DISEASE

Roentgenologists have diagnosed diverticulosis and diverticulitis of the colon since the beginning of this century and we now know that about 10 per cent of all people over the age of 40 have one or more colonic diverticula. Approximately 20 per cent of this group will eventually develop clinical evidence of diverticulitis. Beginning about 1930, the roentgenologic diagnosis of diverticulitis began to be suspect by roentgenologists, gastroenterologists and surgeons and the accuracy is still open to question. Over the period of years, clinicians and surgeons became less dependent on the roentgenologist's report, and modern medical and surgical literature on diverticulitis now contains little mention of the need for roentgenologic help. Roentgenologists have remained divided in their willingness to make a diagnosis of diverticulitis and, of course, our intrinsic problem is: does this lack of agreement harm the patient and is a more uniform opinion justified?

Periodically, published reports have questioned the roentgenologic diagnosis of diverticulitis, but recently Fleischner and his associates^{6,7} have rekindled interest in the problem by reporting a thorough and thoughtful review of a group of patients who were operated on for diverticulitis. They studied the surgically removed specimens, correlated the pathologic and presurgical roentgen findings and presented their concepts of diverticular disease. They highlighted the fact that surgically removed specimens of sigmoid colon frequently fail to show roentgenologically predicted diverticulitis while if the specimen showed diverticulosis and a mass, the tumefaction was due mainly to rupture of one or more diverticula.

In an attempt to evaluate our present knowledge of diverticular disease and to seek an answer to the intrinsic problem, it is most important to be aware that one or more diverticula may exist and fail to be detected at any one colon examination and that clinical diverticulitis can be present, though rarely, and fail to give any roentgenologic finding. A roentgenologic diagnosis of diverticulitis is not apt to result in harm to the patient if we limit our criteria to demonstrable diverticulosis with either intramural extravasation of barium or opacification of a pericolic abscess cavity or fistula. All other changes must be interpreted with caution. Close grouping, apparent separation, asymmetry or deformity of diverticula do not necessarily indicate an inflammatory process. In diverticulosis, persistent swelling of the mucosa, thickening of the colon wall or persistent deformity of the opaque column by extrinsic pressure can only tell the roentgenologist that an abnormal swelling is present. Without complete clinical correlation, he can only guess whether the tumefaction represents an acute, subacute or chronic, persistent or intermittent inflammatory process whether it represents the burnt-out end stage of previous inflammation. Inability of an area of diverticulosis to distend to estimated normal colon diameter, deep haustral markings, or deep peristaltic waves are not pathognomonic of inflammation, for these findings can be a normal response with or without diverticulosis to the retrograde injection of fluid or air and especially so in a hypertonic, frightened patient. If the temperature of the barium suspension is considerably above or below body temperature and/or if the colon is distended rapidly, a similar response may be observed.

In formulating a "new look" regarding diverticular disease of the colon, Almy¹ recently stated that excellent pathologic, radiologic and physiologic studies now solidly support the old ideas that work hypertrophy of colon muscle in the sigmoid area occurs frequently in older people, intraluminal pressures can be high and diverticula form at the anatomic weak areas. It is now obvious that the roentgen

image of "saw-toothed deformity" of the sigmoid is easily correlated with sustained contraction of hypertrophied muscle bundles. The presence or absence of diverticula in such a segment should not change the interpretation of the basic deformity. How interesting it is to go through one's teaching files and find roentgenograms depicting the condition "diffuse spasm of the lower esophagus" and note that some look a great deal like the "saw-toothed" sigmoid. Both conditions occur in the older age groups. may be asymptomatic or produce somewhat similar but segment orientated symptoms and both are characterized by muscle hypertrophy and altered physiology.

Since 1920, The Caldwell Lecture has been one of the main features of the annual meeting of the American Roentgen Ray Society and it is natural to assume that history has claimed many of the previous speakers. In concluding this discussion of diverticular disease I have a special message for you: "Congratulations to the American Roentgen Ray Society and best wishes for a successful annual meeting, your first Caldwell Lecturer, W. C. Alvarez, M.D."

The message continues and Dr. Alvarez recalls that he received his first vertical roentgenoscope from Vienna in 1912 and then began an intensive study of gastro-intestinal physiology. The title of his Caldwell Lecture given in 1920 was "Peristalsis in Health and Disease."

As early as 1925, he recognized that true diverticulitis of the colon was not a clinical entity and seldom encountered pathologically, but rupture of one or more diverticula could produce symptoms and physical findings as well as gross pathologic changes. He assumes the prerogative of seniority and concludes with this advice, "A good roentgenologist should remember that the colon has intrinsic and extrinsic nerve elements and pay particular attention to altered physiology for it may mimic organic disease." The final advice via the postscript is, "Please tell them not to make such long reports."

2. ULCERATIVE DISEASE

When considering ulcerative disease of colon and small bowel, the roentgenologist is aware that a localized, segmental or diffuse inflammatory process may be present but not detectable by his examination. In some instances the disease process is not advanced enough to produce gross change detectable by roentgenologic methods and in others colon debris may obliterate mucosal changes. The limitations of detection in minimal ulcerative disease are again emphasized when the surgeon or pathologist finds the disease more extensive than predicted. These problems are not iatrogenic, but are part of the inherent limitations of the roentgen method. After establishing definite evidence of ulcerative disease, roentgenologists may face the difficult intrinsic problem of classification according to type. Each recognized variety of colitis carries a somewhat different prognosis and the medical or surgical management varies accordingly. A review of some of the background and basic differences between various ulcerative diseases of the colon may help clarify a somewhat confusing picture.

The pioneer roentgenologists were able to recognize common ulcerative colitis and tuberculosis of the ileum and right side of the colon. The changes in tuberculosis were ulcerative, hyperplastic or both and, of course, were characterized by granuloma formation with caseation and necrosis and demonstration of the causative organism. Later, similar cases were observed but pathologists were puzzled when, on examining the granulomas, they could find neither caseation, necrosis nor a causative organism. In 1932 Crohn, Ginzburg and Oppenheimer⁵ reported their observations on this idiopathic disease process and established granulomatous regional ileitis as a clinical entity. About the same time Bargen and Weber² conducted intensive studies on their cases of common chronic ulcerative colitis and firmly established the clinical, pathologic and roentgenologic features of

this disease entity. Their classic descriptions are universally accepted today. These investigators, and others, recognized that about 75 per cent of all cases of chronic ulcerative colitis fit into a rather typical pattern with the disease beginning in the rectum and extending proximally in a continuous and uninterrupted fashion until the entire colon and, at times, the terminal ileum were involved. They noted that, although the disease tended to be progressive, it could remain localized to the rectum or stop at any point in its cephalad progression. This is common chronic ulcerative colitis. The other 25 per cent of their cases included some in which a specific etiologic factor could be found but the disease was idiopathic in most instances. These unusual cases of colitis have provoked a great deal of investigation and some controversy in regard to classification but no real disagreement which might affect the patient.

Bargen and his co-workers prefer the term regional or segmental colitis and define the disease as an idiopathic inflammatory condition of the colon involving one or more segments, exclusive of the rectum, but, at times, including the terminal ileum. The disease may be granulomatous or ulcerative and, if the right colon is involved, Neuman and Dockerty¹¹ report that up to 40 per cent will have involvement of the terminal ileum.

Following Crohn's report in 1932, others began to find that this granulomatous disease could involve other segments of the small bowel as well as the colon. While the term "Crohn's disease of the colon" was adopted in England, Wolf and Marshak²¹ in this country emphasized the granulomatous nature of the disease process and have reported excellent studies on the clinical, roentgenologic and pathologic aspects of this unusual colitis.

The astute clinical roentgenologist usually has no great difficulty distinguishing between the common chronic ulcerative colitis and segmental or granulomatous colitis but, at times, complete clinical correlation is not decisive and pathologic ex-

amination is necessary. The examination for either of these two types of colitis is not complete without an adequate small bowel investigation and when there is evidence of right-sided colitis, without gross change in the terminal ileum, and either with or without skip areas elsewhere in the colon, amebic colitis must be ruled out. There is nothing pathognomonic about the roentgenologic findings in this specific disease. Any stage of ulceration or granuloma formation may be present in the cecum. Demonstrable skip areas simulate idiopathic disease and there may be rectal ulceration and peri-anal involvement. Rarely, the disease may present in an acute fulminating form with clinical and roentgenologic findings almost identical to the acute toxic megacolon complication of common chronic ulcerative colitis. Time does not permit discussion of other rare forms of chronic ulcerative colitis.

When one or more of the various manifestations of ulcerative disease appear to be demonstrated by very minimal roentgenologic findings, even the most experienced examiner may have difficulty interpreting the changes. Occasionally, a segment of opacified colon will show numerous, closely spaced, shallow and pointed ulcer-like projections which are merely normal mucosal grooves visualized tangentially. If visualized en face, these grooves present as an irregular patch work which can simulate the granular type mucosa of common chronic ulcerative colitis. The absolute regularity of the defects and the absence of other signs of true ulcerative disease usually establish the nature of these minute projections, but, in case of doubt, re-examination the next day fails to confirm their presence in the same area. The reason for this occasional and inconsistent spiculation is somewhat obscure but one may theorize that the mucosa of a short segment happens to be exceptionally free of mucus and cellular debris so that the barium suspension can be in intimate contact with the mucosa and thus able to fill the clean grooves. Shallow mucosal ulceration and slight bowel wall thickening may appear

to be present when certain types of nonformed fecal residue are noted. Evacuation and re-introduction of barium or re-examination the next day usually clarifies this problem. The ability to resolve these difficulties does not imply the right to ignore all minor changes. It is not rare for an experienced examiner to encounter minimal roentgen findings in a patient who has no clinical or laboratory evidence of ulcerative disease but in whom the process eventually becomes clearly evident. The recent report of Welch and Hedberg²⁰ substantiates some of this concern when they state that surgical and autopsy findings indicate that many patients with chronic ulcerative colitis are totally asymptomatic so that no one knows how many patients may have a mild form of this disease. In contrast to the difficulties encountered when there is only minimal evidence of ulcerative disease, it is worth mentioning that occasionally a roentgenologist may find definite evidence of moderate or advanced disease, usually segmental, with no support from the patient's history, physical examination or laboratory studies. Severe disease does not always imply severe symptoms and, instead of diarrhea and bleeding, the patient may complain only of constipation.

While close inspection of the roentgen details of mucosal ulceration and bowel wall deformity may help, the over-all gross appearance of the colon and terminal ileum is apt to be more reliable for proper classification. Definite changes presenting in a characteristic roentgen image may provoke a feeling of diagnostic competence in the experienced and well informed roentgenologist but the findings are not always typical, exceptions are not rare and a feeling of trepidation may be proper and commendable.

The detection and subsequent classification of ulcerative disease are of such great significance to the patient that the roentgen findings and diagnosis should seldom stand alone and must be correlated with the history, clinical and laboratory findings.

3. NEOPLASTIC DISEASE

Unlike ulcerative disease of the colon. clinical correlation or any other substantiation is not necessary if a roentgen detected lesion fulfills the Weber-established criteria for frank carcinoma.18 Some difficulty in interpretation may arise when the characteristic image of a polypoid or annular constricting carcinoma is altered by chronic gross perforation. Again, we are indebted to Weber¹⁹ for explaining this complication in terms of the roentgen findings. Later, in 1952 and again in 1953, Sommer and I confirmed¹³ Weber's observations and emphasized that demonstration of a fistula or abscess cavity extending out from an area of carcinoma is evidence of advanced disease, but the most frequent finding is deformity of the barium column by an extracolic mass. This mass is composed of any combination of malignant or inflammatory tissue and, like the pericolic mass of complicated diverticulitis, causes an extrinsic pressure defect on the colon lumen. Differential diagnosis is based on the fact that, irregardless of the deformity produced by the mass, all of the roentgen criteria for malignancy are not lost.

In contrast to the few problems we have with frank carcinoma of the colon, the detection and diagnosis of small polypoid lesions are accompanied by many difficulties. Early in my experience with the colon examination, I was most fortunate to have as associates Dr. Robert D. Moreton and Dr. Everett E. Seedorf. We had the same radiologic background and a mutual Weberinspired interest in the colon examination. One of our first departmental efforts was an attempt to standardize the double contrast examination so that we, as well as others, might find it more consistent and reliable.¹⁵

We conducted studies on the roentgen characteristics of small polyps, their differentiation from grossly similar but fictitious polyps¹⁴ and determined clinical indications¹⁶ which lead to the discovery of more small lesions. Others sought different methods for detection of small neoplasms. Wyatt²² recommended use of tannic acid in the barium suspension, Gianturco⁸ favored

a high kilovoltage technique while some preferred the use of a more dilute or less opaque suspension. Also advocated were careful fluoroscopy and multiple spot roent-genograms. In the near future, Wyatt will report on his investigations of a tannic acid substitute.

The widespread interest in methods of detection led to more transabdominal removal of polyps with incidental discovery of others which had escaped detection. As of today, no roentgenologic method will ensure a polyp prevalence rate equal to that determined by autopsy findings. Our problems are compounded by such opposing statements as, "Half of the people we operated on for a polyp had more than the roentgenologist predicted,"-"A competent radiologist with good equipment is now able to recognize any lesion of the colon that is 5 mm. or larger, in almost every case," "Preoperative radiological studies, repeated at least once before laparotomy, have been so accurate that we find it unnecessary to look for additional polyps at the time of surgery." The bright crown of achievement may be tarnished by appreciation that undetected adenomas may never make their presence known while the humiliated roentgenologist may have encountered too many problems beyond his control.

In spite of the controversy over the pathologic significance of the small colon polyp, the fact that a I cm. adenoma and a I cm. carcinoma can have the same roentgenologic appearance makes it necessary for us to continue our search for small lesions. Many will agree with Cooley4 that in polyp hunting, the experience and thoroughness of the roentgenologist are more important than the technique employed. Another problem is indicated by the fact that many roentgenologists feel that the method they use for detection of small polyps is not completely satisfactory for all other diseases of the colon and terminal ileum. It is seldom that a roentgenologist can say that on any one examination he can detect or rule out minimal ulcerative disease as well as small polyps anywhere in the colon and terminal ileum. Economic loss, patient discomfort and delay can usually be avoided if the pre-examination requirements are fulfilled.

ACCURACY

While the patient may be adversely affected by roentgenologic error in diverticulitis or ulcerative disease, his life may be at stake if the problem is neoplastic disease. Various investigators^{3,10} quote roentgen diagnostic errors of omission as being in the vicinity of 10 per cent. These figures are for frank carcinoma and nobody knows the rate for small polypoid carcinomas. Roentgenologists are aware that gross lesions in the cecal and sigmoid areas may be overlooked or difficult to demonstrate, but a good part of the 10 per cent error is human failure to see an obvious deformity. Many physicians are not aware of the very real difficulties and limitations associated with the colon examination and accept the colon report without question. I would like to suggest that the following statement of estimated accuracy be added to every roentgenologic report:

COLON EXAMINATION-ESTIMATED ACCURACY

terminal ileum <i>not</i> included	i	
proctoscopic report not receiv	red	[
A. For Inflammatory Disease		
Minimal-moderate-severe	•	
50% or less	()
plus or minus 70%	()
plus or minus 90%	()
B. For Neoplastic Disease		
Under-over 1 cm.		
50% or less	()
plus or minus 70%	()
plus or minus 90%	()
C. Related to Main Clinical In	dic	ation
50% or less	()
plus or minus 70%	Ċ)
plus or minus 90%	()

Note: Cross-out or check-mark the appropriate words or spaces to emphasize the true significance of the report. It is seldom that plus 90% can be checked.

There are many obvious benefits to be obtained from the routine use of an estimated accuracy form but caution is indicated if it is to be used for statistical purposes. The "mystic statistic" is another of our many problems.

TERMINOLOGY

Throughout this discussion I have intentionally omitted the use of the term "barium enema." Webster's definition of enema is "a liquid injected into the rectum as a medicine or purge or to impart nourishment." When pioneers in roentgenology substituted insoluble barium sulphate in place of the medication, they coined the term "barium enema." Today, the term is not desirable. Patients associate "enema" with expected therapeutic action and many physicians think that a barium enema followed by some "pictures" will result in an accurate diagnosis. Such statements as "order a barium enema," "what did the barium enema show?" and "what were the results of the barium enema?" fail to recognize the role of the roentgenologist and imply that the procedure is mechanical, automatic and standardized. Of course, this is not true but continued use of the term can only delay recognition that the diagnostic procedure is a physician's method of indirect physical examination. Preferred terms are "colon examination" or "barium enema examination" and I hope roentgenologists can lead the way to their general acceptance.

When communicating his findings to others, the roentgenologist does not enhance the status of the colon examination by continued use of nonmedical descriptive terms such as napkin ring, apple core, prune pit, target sign, bullseye sign, hat sign, string sign, cushion sign, antler sign, etc. These terms are confusing to other physicians and suggest that the roentgenologist employs a crystal ball, tea leaves or signs of the Zodiac in arriving at an anatomic diagnosis. Since the purpose of the examination is to detect the presence or absence of disease, any abnormalities found must be

described in the generally accepted terminology used by the pathologist.

CONCLUSIONS

The colon examination is of great importance in the health care of our people and its value can be increased by a wider understanding of the attendant difficulties and limitations. Fulfillment of certain pre-examination requirements unfetters the roentgenologist and permits his best diagnostic effort. If he conveys the full significance of his findings to the referring physician, the patient most assuredly will benefit.

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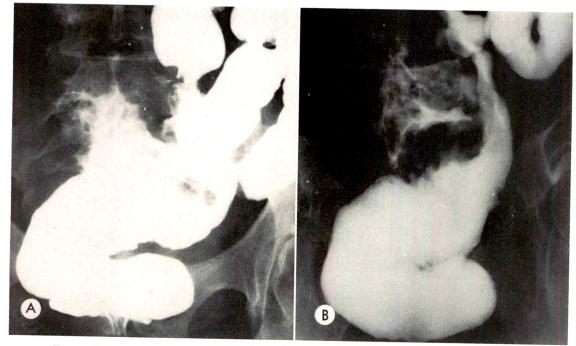


Fig. 4. Roentgenograms of a patient with large perforating carcinoma of the rectosigmoid colon. (\mathcal{A}) Anteroposterior view. (\mathcal{B}) Angled view.

and angling the roentgen-ray tube, but sizable studies which actually document the value of such angled roentgenography have not been reported. To establish the significance of our special angled view in

visualizing lesions of the rectosigmoid, the clinical material accompanying 16,620 roentgenographic examinations of the colon with barium enema was reviewed. This 5 year survey from 1959 through 1963

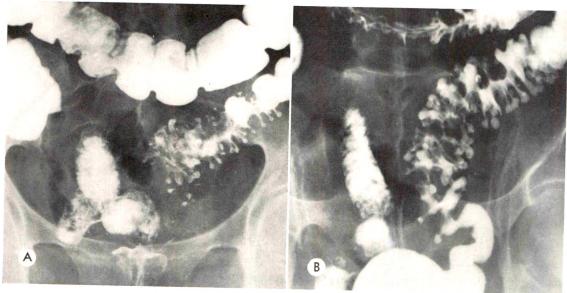


Fig. 5. Roentgenograms showing diverticulosis with evidence of old diverticulitis. (A) Anteroposterior view. (B) Angled view.

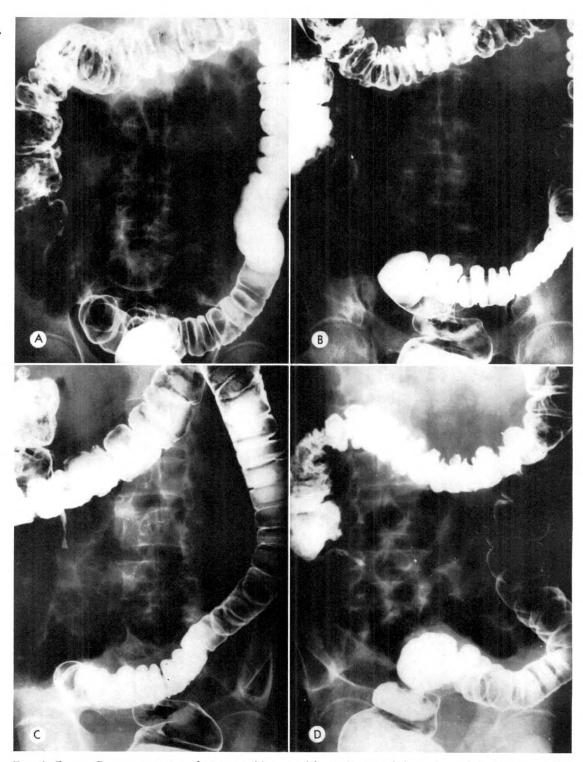


Fig. 6. Case 1. Roentgenograms of 58 year old man with carcinoma of the rectum. (A) Anteroposterior view. (B) Posteroanterior view. (C) Left anterior oblique view. (D) Right anterior oblique view.

yielded 5,217 positive diagnoses for 3,419 patients (Table 1).

In this series of roentgenograms made during examinations employing the barium enema, the angled view was used routinely with 2,223 air contrast studies because of the frequency in which it is of definite value for delineating and locating polyps and other lesions of the rectosigmoid (Fig. 2 through 5, inclusive). Also, 390 additional angled roentgenograms were obtained of the barium filled or evacuated colon, making a total of 2,613 special studies (Table II).

On the roentgenograms employing the special angled view, 314 lesions involving the rectum and/or sigmoid were visible; and when all available roentgenograms of these patients were scrutinized, it was concluded that the special angled view was of definite value for delineating 81 of the 314 lesions. Of special importance was the fact that during the 5 year period, 35 patients with proved carcinoma of the rectum, all with lesions which were less than 16 cm. above the anal verge, had examinations employing the barium enema—and 34 of these malignant lesions could be seen clearly on the angled roentgenograms.

DISCUSSION

The authors do not wish to imply that angled roentgenography represents a new technique. Although our review of the available medical literature could not establish exactly when angled views of the rectum and sigmoid began, it seems that the idea originated many years ago because the early fluoroscopists stressed rotation and positioning of patients.

At this institution, the special angled view of the rectosigmoid region first was used in 1953 by a former member of the staff, and it was called the "see more" view.* Since that time, this view has been used often, but has not been employed routinely. The decision for ordering the special view generally is made during fluoro-

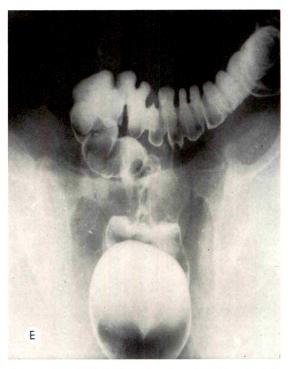


Fig. 6. (E) Angled view showing the lesion in full.

scopic examination when visualization of the rectum and sigmoid proves to be difficult. This problem was emphasized dramatically by 2 recent cases.

ILLUSTRATIVE CASES

Case I. When a 58 year old man was examined proctosigmoidoscopically, an annular carcinoma of the rectum, beginning 12 cm. above the anal verge, was revealed. However, when he was examined fluoroscopically in many positions, the lesion could not be visualized. On the routine posteroanterior, anteroposterior, and oblique roentgenograms (Fig. 6, A–D), the tumor was suggested, but its exact nature and extent were not disclosed. Fortunately, the angled view showed the lesion in its fullest extent (Fig. 6E).

The patient has done well postoperatively. Subsequent examinations have revealed a normally functioning anastomosis, and recurrence of the carcinoma is not evident. Had this patient not been examined proctosigmoidoscopically, his lesion would have been missed fluoroscopically, and without the special angled view his malignant tumor might have been overlooked entirely. The impact of this case

^{*} Introduced by Dr. Everett E. Seedorf, now in practice in Peoria, Ill.



Fig. 7. Case II. Roentgenograms of 47 year old woman with extensive metastasis secondary to carcinoma of the cervix. (A) Anteroposterior view. (B) Posteroanterior view. (C) Left anterior oblique view. (D) Right anterior oblique view.

prompted this study. Case II illustrates a similar problem.

Case II. In the fall of 1963, a 47 year old woman developed partial obstruction of the sigmoid colon due to metastatic implants from carcinoma of the cervix diagnosed in 1960. The involved segment of the colon was resected, and the patient seemed to do well until February, 1964 when signs of obstruction reappeared. When air contrast studies (Fig. 7, A-D) of the colon were performed, an annular appearing lesion in the midsigmoid colon was visible only on the angled roentgenogram (Fig. 7E). Subsequent laparotomy revealed extensive metastases secondary to carcinoma of the cervix.

Another value of angled roentgenography is the accuracy with which measurements can be made directly on the roentgenograms. During proctosigmoidoscopy in 1959 and 1960, hemostasis clips were placed on selected polyps of the rectum and the sigmoid and their distance from the anal verge was measured. After air contrast studies, the measurements were repeated by measuring the distance directly on the angled roentgenograms. Also, angled roentgenography can be especially advantageous when used to expose the pelvic cecum and in instances where the terminal ileum has filled with barium and overlies the loops of the sigmoid colon.

SUMMARY

At the Scott and White Clinic, special angled roentgenography has proved valuable for detecting elusive lesions of the rectosigmoid. During the 5 years from 1959 through 1963, the 16,620 roentgenographic examinations of the colon employing the barium enema yielded 5,217 positive diagnoses for 3,419 patients. The angled view was ordered 2,613 times. This

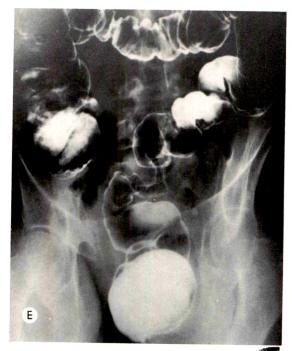


Fig. 7. (E) Angled view showing an annular appearing lesion in the sigmoid colon.

special view provided delineation for 81 of 314 lesions of the rectosigmoid region, and 34 of 35 proved carcinomas of the rectum could be seen clearly. Also, the distance of each lesion from the anal verge could be measured on the roentgenogram.

Angled roentgenograms of the rectosigmoid region are not suggested as satisfactory substitutes for proctosigmoidoscopy. The special view, however, will serve as a diagnostic adjunct when a lesion has been reported by the proctologist. The technique should be helpful, perhaps even conclusive, in those medical practices without extensive diagnostic facilities.

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THE USE OF A WATER ENEMA IN THE VERIFICATION OF LIPOMA OF THE COLON*

By G. MELVIN STEVENS, M.D. PALO ALTO, CALIFORNIA

THE suspicion of submucous lipoma of the colon may be raised by such polypoid mass features as smooth outline, sessile contour, radiolucency and variability of shape, but the true diagnosis has often been speculative until the lesion has been removed. With the use of a water enema and high contrast roentgenography one can, however, preoperatively establish the diagnosis of submucous lipoma.

That such a procedure was theoretically applicable and practically useful was described by Margulis and Jovanovich³ in 1960. Their report included splendid *in vitro* and *in vivo* experiments using simulated polyps with the density of air, water, and gas. These were studied by using barium, air, double contrast, and water as contrast substances with 30, 60, and 90 kv. exposures. The combination of a water enema and low kv. exposures took best advantage of the difference in energy absorption between the fat of the lipoma and its surrounding substance, and thereby allowed its identification.

The positive identification of a lipoma of the colon may spare certain patients the unnecessary risk of surgery, and in others indicate the feasibility of local excision. This method was employed by Margulis and Jovanovich and the diagnosis of lipoma established in 2 patients, but confidence in the radiologic diagnosis forestalled surgery.

Judging from the absence of other reports on the use of water enema, it seems that the method is not well known and deserves further mention. The following report of 2 surgically verified cases confirms the reliability of the method.

REPORT OF CASES

Case I. A 70 year old female complained of bloody diarrhea which had for years been re-

curring at approximately 6 month intervals. One month prior to admission, she had experienced severe diarrhea with 10 to 12 blood and mucus streaked bowel movements daily, accompanied by cramping left lower quadrant pain.

There was no weight loss and no mass was palpable in the abdomen. Rectal and sigmoid-oscopic examination revealed proctitis with a dry mucosa which bled rather easily. Moderate spasm of the sigmoid was encountered.

A subsequent barium enema study was performed and a smooth-bordered, obstructing mass measuring 9×6 cm. was found in the lower descending colon (Fig. 1, A and B). Although only a small amount of barium passed by the mass, its smooth margin, size and location suggested the possibility of a lipoma. No discernible radiolucency of the mass was present (Fig. 2). One day later, after additional preparation, a water enema was given, whereupon the lipomatous nature of the mass was confirmed roentgenographically. Figure 3, A, B and C shows balanced exposures which were made using 60, 85, and 120 kv. These clearly illustrate the utility of low kv. exposure, though this large lipoma can be seen in all 3 roentgenograms.

At surgery, the tumor was seen attempting to intussuscept. The bowel was greatly hypertrophied immediately below the mass, apparently reflecting the attempt of the lower bowel to pull the lipoma down and expel it. Above the tumor, the bowel was normal. Several small mucosal ulcerations were present on the surface of the tumor (Fig. 4, A and B). Local resection was easily carried out.

Case II. Two days prior to admission, a 57 year old male complained of moderately severe, diffuse, abdominal pain and slight constipation. Five days earlier he had had postprandial indigestion with "diffuse abdominal discomfort." He had taken antacid and at times tranquilizer medication for relief of occasional, less severe, episodes of abdominal discomfort during the prior 2 years. Infrequent, slight rectal bleeding had been noted for at least 4 years and

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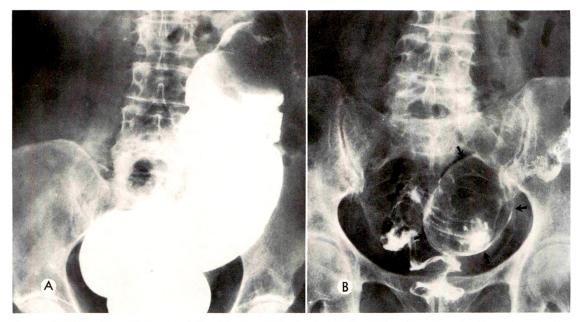


Fig. 1. (A) An obstructing smooth bordered mass in the descending colon is seen on barium enema study. (B) The size, contour and shape of the mass are well demonstrated in the postevacuation roentgenogram.

had been attributed to the internal hemorrhoids which were present. A barium enema study performed 2 years before had been erroneously interpreted as being normal.

The past history included the removal of a lipoma from his back 18 years previously, and the resection of an adenomatous polyp of the rectosigmoid 12 years ago.

On physical examination, a right upper quadrant mass was believed palpable, but on the following day it had disappeared.

Barium enema study established the presence of a smooth-bordered, large, somewhat mobile, mass attached to the medial wall of the ascending colon just above the expected level of entry of the terminal ileum (Fig. 5, A and B). A submucosal lipoma seemed likely and the next day, after further preparatory enemas, a diagnostic water enema study was made. The



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Fig. 2. Despite its size, the large lipoma cannot be recognized by its radiolucency on barium enema roentgenograms.

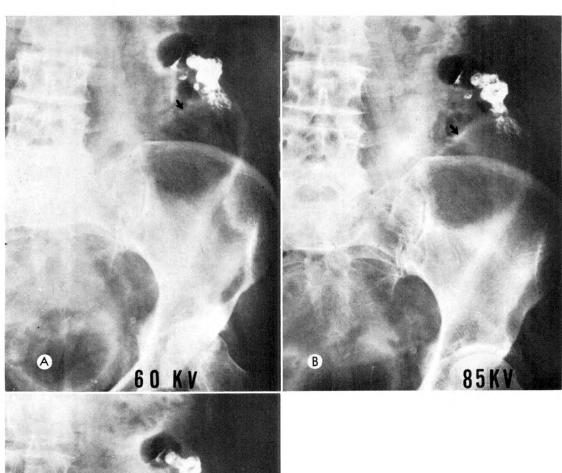




Fig. 3. After a water enema, roentgenograms taken at (A) 60, (B) 85 and (C) 120 kv. confirm the submucous lipoma and demonstrate the superiority of low kilovoltage technique.

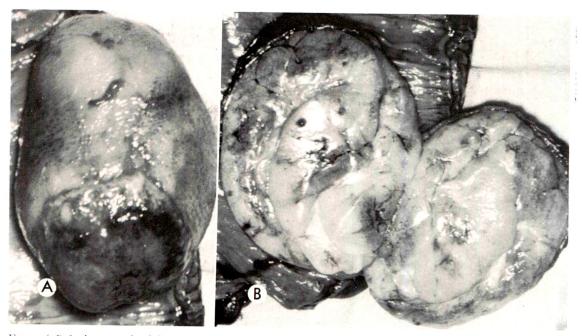


Fig. 4. (A) A photograph of the intact tumor shows several small ulcerations of the covering mucosa. (B) The cut specimen reveals the uniform benign fatty character of the tumor.

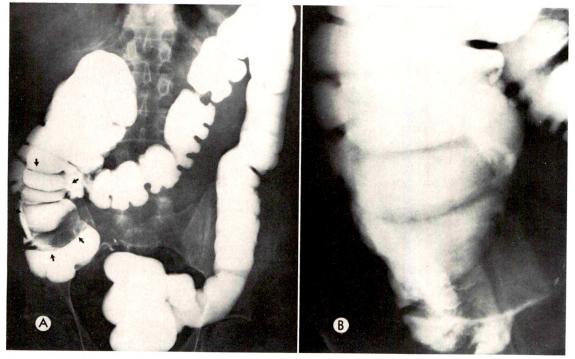


Fig. 5. (A) A large smooth-bordered ascending colon mass is seen in the barium filled colon. (B) Radiolucency in the mass is not appreciated on a spot roentgenogram.

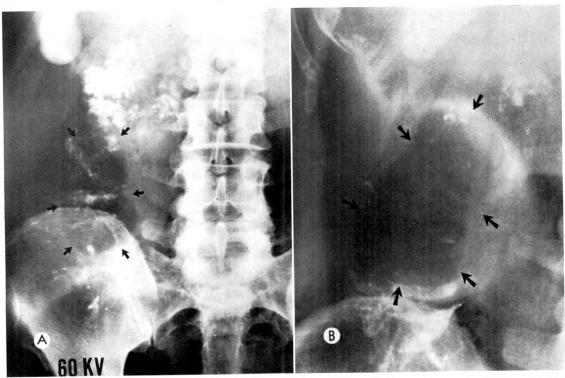


Fig. 6. (A) A water enema study clearly demonstrates the lipoma. Slight movement of minimal residual barium assists in fluoroscopically controlling filling. (B) A localized view provides improved detail of the lipoma-water interface.

persistent large radiolucency conforming to the previously demonstrated mass left no doubt as to the lipomatous nature of the tumor (Fig. 6, A and B). The small residue of barium remaining after the preceding barium enema examination moved slightly as water filling occurred, thus assuring adequate filling of the segment in question.

Subsequent surgery, with the preoperative diagnosis established, permitted a submucosal local excision of the 8.6×5.5×4.5 cm. tumor. Two or three small mucosal ulcerations overlying the lipoma undoubtedly accounted for the history of occasional bleeding (Fig. 7).

DISCUSSION

Of the benign tumors of the colon, lipomas are second in frequency only to adenomas. The average age of patients at the time of discovery of lipomas of the colon is 60 to 65 years. Approximately 90 per cent of colon lipomas are submucous, while 10 per cent are subserous.² A water enema study is principally, and perhaps only, of

value in the verification of the submucous variety. The fact that few lipomas are diagnosed preoperatively, either on plain roentgenograms or barium enema studies, is clear from the reports of Ginzburg et al.1 and Wychulis et al.5 In the former report only 3 of 19 lipomas were correctly identified and, in the latter, only 4 of 67 were recognized as lipomas preoperatively. The reason for this is the minimal radiation absorption differences between fat and the tissue of the surrounding viscera and its content in the conventional higher kv. range of diagnostic radiology. The difference in linear absorption coefficient between fat and muscle is nearly twice as great at 60 kv. as it is at 125 kv. The absorbed dose in ergs/r is onethird greater at 60 kv. than at 125 kv.4

The importance of definitive preoperative identification is obvious in any patient who has a contraindication to surgery. Many lipomas are discovered only incidentally or, in fact, accidentally, 1,5 and

produce no symptoms. The necessity for removal of all such asymptomatic tumors might be debated. None has been known to undergo malignant transformation. In others which require surgery because of obstruction or bleeding, the lipoma may have gross features obligating the surgeon to treat the tumor as a malignancy. Ten of 38 Mayo Clinic patients undergoing surgery primarily for a colon lipoma had a hemicolectomy performed because of the uncertainty of the nature of the tumor.5 Cancer type bowel resections were performed for the same reason on 6 of 19 colonic lipomas seen at the Beth Israel Hospital of New York.5

The preoperative confirmation of a lipoma by the use of a tap water enema study provides for a much more prudent decision as to whether surgery is a necessity in poor-risk patients and indicates that a local excision will suffice in those patients requiring surgery.

SUMMARY

Two cases are reported which demonstrate the practicality of using a tap water enema and low kilovoltage exposures as a means of confirming the presence of a submucous lipoma of the colon. This combination of contrast and exposure magnifies the small radiation absorption differences of fat and water density tissue. Once identified as a lipoma, more confident and conservative management can be planned.

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Fig. 7. Several tiny mucosal ulcerations are seen on the surface of the locally excised lipoma.

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GARDNER'S SYNDROME

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GARDNER and Richards² in 1953 described a triad of subcutaneous tumors, osteomas and large bowel polyposis in many members of a large family. Although about 40 cases of the complete Gardner's syndrome have been reported since that time, only I article has appeared in the radiologic literature⁶ and this dealt mainly with the bone changes. The patient reported in this paper had surface features which were not striking but readily evident when they were specifically sought.

REPORT OF A CASE

A 64 year old white man consulted his private physician with a 5 week history of loss of appetite, a sensation of fullness in the upper abdomen associated with intermittent gas pain and a weight loss of 7 pounds. He had no symptoms referable to the bowel but 5 years previously he had been hospitalized in Trieste for "colitis" which responded to medical treatment.

Physical examination revealed a pale man with a rather tense abdomen. No mass was palpable on abdominal and digital rectal examination and the general examination was unremarkable.

An upper gastrointestinal series showed no abnormality. On barium enema examination there were innumerable rounded filling defects, 2 to 7 mm. in diameter throughout the large bowel (Fig. 1). A constant narrowing, 3 cm. long, was present in the right transverse colon, just beyond the hepatic flexure (Fig. 2). Before the patient left the x-ray department, he was examined and a pedunculated soft tissue tumor, 3 cm. long and 0.5 cm. in diameter, was noted arising from the skin over the midsternal region. Palpation of his head revealed 3 hard lumps in the right frontal region, the largest being 1.5 cm. in diameter and 0.5 cm. high. Skull roentgenograms (Fig. 3 and 4) showed these to be osteomas.

The diagnosis of Gardner's syndrome with

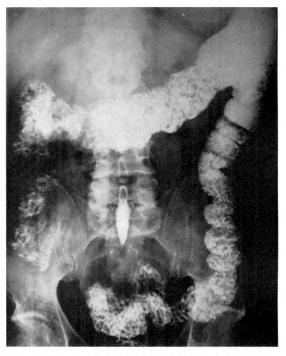


Fig. 1. Innumerable polyps, 2 to 7 mm. in diameter, are evenly scattered throughout the large bowel. Contrast medium from a previous myelography is seen in the spinal canal.

malignant change in the right transverse colon was made.

The patient was admitted to hospital and a laparotomy was performed. A mass was found in the right transverse colon adherent to the surrounding structures. On dissection an abscess cavity was entered and as the frozen section showed no carcinoma an ileocolostomy was performed. Inspection of the bowel distal to the narrowing showed multiple polyps, some of which were excised. Histologic examination of 5 of these showed invasive adenocarcinoma in one and precancerous changes in the other adenomas.

The postoperative recovery and wound healing were slow but he was discharged after 3 weeks, only to be readmitted 5 days later with

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Fig. 2. An oblique roentgenogram shows a short region of narrowing in the transverse colon projected just to the right of the spine. This was diagnosed as carcinoma and confirmed at autopsy.

vomiting, diarrhea, dehydration and toxemia. There was no abdominal distention but severe lower limb edema and clubbing of the fingers were noted. The serum sodium was 120 milli-



Fig. 3. A lateral roentgenogram of the skull shows 3 rounded densities in the frontal region.

equivalents per 100 ml., the potassium 2.7 milliequivalents per 100 ml., the albumin 0.6 gm. per 100 ml., and the globulin 2.0 gm. per 100 ml. Concentrated serum albumin, 800 gm., was given in 5 days and the serum albumin rose to 1.9 gm. per 100 ml. and then remained between 1 and 2 gm. per 100 ml. A 24 hour collection of urine showed no protein. The fecal fats measured 8 gm. in 24 hours.

The possibility of a protein losing enteropathy was considered and an I¹³¹ human serum albumin turnover study was performed. The metabolic degradation rate was 37 mg. per kg. per day (normal 220 mg. per kg. per day) and the biologic half life was 50 days (normal 12 to



Fig. 4. A tangential roentgenogram of the largest lump palpated in the right frontal region shows a broad based osteoma.

17 days). This indicated that there was no abnormal protein loss from the body. The very slow turnover of albumin suggested an abnormality in the mechanisms of synthesis.

The patient developed progressively more active borborygmi followed by diarrhea and vomiting. Intravenous fluids were given to combat the resulting dehydration. A few days later he developed acute retention of urine which persisted when the urethral catheter was removed and a transurethral resection of the prostate was done under local anesthesia. He then developed septicemia and despite antibiotic and supportive therapy died 4 days later.

Autopsy showed innumerable polyps throughout the large bowel and an ulcerating carcinoma, 6×8 cm., in the right transverse colon. There were no hepatic metastases. Multiple infarcts and small abscess cavities were found scattered in the lungs.

As far as the patient knew, neither his parents, who were deceased, nor his two sisters and one brother, who lived in Trieste, had bowel complaints. His only daughter had no surface manifestations of Gardner's syndrome or bowel symptoms. She refused the barium enema examination.

DISCUSSION

Familial polyposis is a hereditary dissease, transmitted as a mendelian dominant autosomal heterozygous gene to males and females alike. Although in most families about 50 per cent of the children inherit the disease, it is occasionally passed on with lack of penetrance or perhaps as a recessive trait. Gardner's syndrome, whether complete or only showing one of the two surface traits, is seen in males about twice as commonly as in females. This consideration, as well as a study of phenotypic differences, raises the possibility that the gene of Gardner's syndrome is distinct from that of familial polyposis, though if there are different genes for the two entities they are probably allelic. However, Smith⁸ believes that Gardner's syndrome is merely the full blown manifestation of a spectrum of pathologic changes which could affect, in variable numbers and combinations, any patient with multiple polyposis. This variability, as well as the apparent anticipation

noted by some workers, can be explained by variable penetrance. Further linkage studies are required before a decision is possible on these two viewpoints.

Most cases of familial polyposis are diagnosed between the ages of 15 and 40 years, the range being 3 to 58 years. The present case is the oldest so far reported.

The incidence of Gardner's syndrome in patients with familial polyposis has been investigated in only one study in which 17 of 201 patients with large bowel polyposis exhibited one or both surface manifestations. Although in the great majority of cases of Gardner's syndrome the polyps are confined to the large bowel, polyps have rarely also been described in the small intestine and these, unlike the polyps in the small and large bowel of the Peutz Jegher's syndrome, are premalignant.

Occasionally, the roentgenographic appearances of familial polyposis may be mimicked by those of lymphosarcoma of the colon, protein losing enteropathy and an uncommon case of ulcerative colitis where the inflammatory process heals completely with reversion of all the roentgen changes to normal except for persistence of a large number of inflammatory polyps. In the latter case, even the pathologist may have difficulty in making an accurate diagnosis. During the course of familial polyposis, at least one of the polyps will become malignant and, if not removed, cause the patient's death. It is, therefore, mandatory to make an unequivocal diagnosis and to avoid a false diagnosis of familial polyposis, which necessitates a total colectomy. If the features of Gardner's syndrome are present the diagnosis is certain. Moreover, any patient who has osteomas of the skull or facial bones with or without desmoid tumors of the skin requires evaluation of the large bowel. It is axiomatic that the relatives of any patient with familial polyposis should be persuaded to have a barium enema examination and preferably also a sigmoidoscopy. If these investigations are negative, they should be repeated every 5 years or if bowel symptoms develop.

SPECIAL ANGLED ROENTGENOGRAPHY FOR LESIONS OF THE RECTOSIGMOID

FIVE YEAR SURVEY, 1959–1963

By DONALD N. DYSART, M.D.,* and HOWARD R. STEWART, M.D.† $_{\rm TEMPLE,\ TEXAS}$

ALTHOUGH the region of the rectosigmoid usually is considered in the domain of the proctologist or of other physicians capable of competent proctosigmoidoscopy, at Scott and White Clinic only 72.8 per cent of the patients who reported for roentgenologic evaluation of the colon during the 5 years from 1959 through 1963 had been examined proctosigmoidoscopically. Because this percentage of patients may be even lower in medical practices without extensive diagnostic facilities, the radiologist should use every available means to examine this important area.

The purpose of the authors is to present a useful adjunct to the roentgenographic diagnosis of lesions of the rectosigmoid—an area which, admittedly, is difficult to examine. Adequate visualization of the sigmoid, so appropriately called a "tangled festoon" by Dr. Harry Weber, has pre-

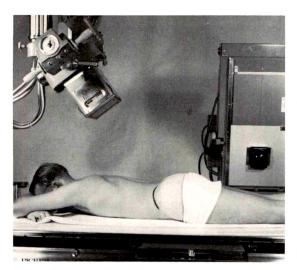


Fig. 1. Position of patient and roentgen-ray tube for producing the angled view. (Technical factors: 100 kv., 100 ma., 1-2 sec.)

TABLE I

ANALYSIS OF 5,217 ROENTGENOGRAPHIC DIAGNOSES MADE FOR 3,419 PATIENTS DURING EXAMINATIONS EMPLOYING THE BARIUM ENEMA*

SCOTT AND WHITE CLINIC 1959–1963

Diagnosis	No. of Patients
Diverticulosis	2,827
Diverticulitis	193
Chronic Ulcerative Colitis	166
Tumors, Benign (polyps)	343
Tumors, Malignant	184
Multiple Conditions in Same Patient	294

^{*} Diagnosis made more than once for some patients.

cipitated many trying moments for the radiologist.

METHOD AND MATERIALS

A special angled view of the region of the rectosigmoid is obtained by placing the patient in the prone position on a standard table with the roentgen-ray tube centered on the lumbar spine at the level of the iliac crest, the tube being angled 30 to 35 degrees caudad, depending upon the patient's thickness (Fig. 1). This technique neither

Table II

SPECIAL ANGLED ROENTGENOGRAPHY
SCOTT AND WHITE CLINIC 1959–1963

Criteria for Special Technique	No. of Studies
Made Routinely with Air Contrast Studies	2,223
Ordered at Fluoroscopy for Delineation of Barium Filled or Evacuated Colon	390
Total	2,613

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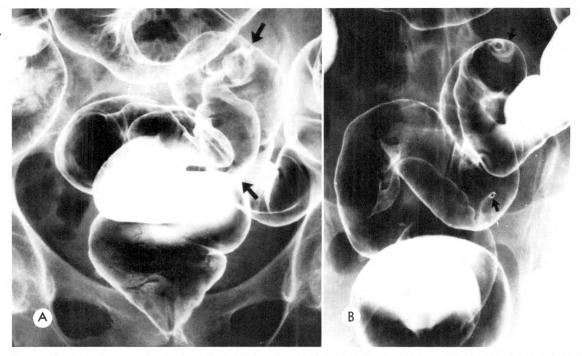


Fig. 2. Roentgenograms showing two pedunculated polyps. A hemostasis clip is attached to the more distal polyp. (A) Anteroposterior view. (B) Angled view.

requires significant time nor does it suggest that the patient assume an uncomfortable position. The resulting roentgenogram usually affords a view of the rectum and of the

sigmoid colon unobstructed by overlying loops of bowel.

The medical literature contains numerous methods for positioning the patient

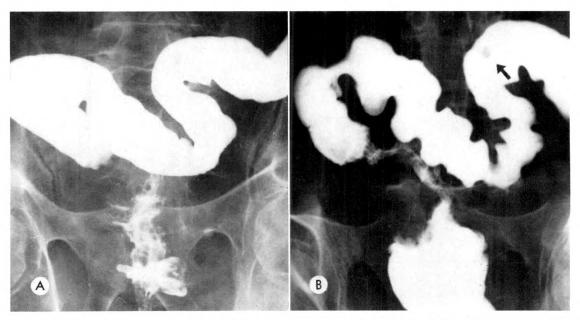


Fig. 3. Roentgenograms of a patient with annular carcinoma, diverticulosis, and a pedunculated polyp, 1×1.5 cm. Arrow denotes polyp. (A) Anteroposterior view. (B) Angled view.

SUMMARY

- 1. A case of Gardner's syndrome is reported.
- 2. The roentgenographic appearances of familial polyposis are occasionally simulated by other diseases but if surface manifestations of Gardner's syndrome are present the diagnosis can be made with certainty.
- 3. Any patient with osteomas of the skull or facial bones requires investigation of the large bowel.

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I wish to express my thanks to Dr. J. Freidin, who referred the patient to me and made the clinical notes available, and Dr. J. Hansky, who performed the I¹⁸¹ human serum albumin turnover studies.

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ROENTGEN FEATURES OF METASTASES TO THE COLON*

بلغثها بالميلان ويتأبه إلى

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ETASTATIC disease to the colon like metastatic disease to the small intestine shows a variety of roentgen changes which may be diagnostic.7 Wigh and Tapley¹⁰ recognized its frequency and described many of the roentgen features. Roentgen changes in the rectum and sigmoid colon involved by carcinoma of the prostate were described by Becker. Additional reports have appeared sporadically.2-5,8,9 Because metastases to the colon occur frequently, consideration of their presence is important in the differential diagnosis of segmental lesions of the colon. Recognition is especially useful when a primary tumor has not been identified. The most common sites of origin are stomach, pancreas, ovary, breast, lung and kidney. The symptoms are generally nonspecific. Abdominal masses and ascites are frequent in the later stages.

Pathologically, the lesions may involve the colon by hematogenous or lymphatic routes or by direct extension. Unlike the small bowel, direct extension by continuity or by lymphatic invasion is frequent, such as carcinoma of the stomach or pancreas metastasizing via the mesocolon to the transverse colon, or carcinoma of the ovary to the sigmoid. Many of the lesions are associated with a desmoplastic reaction and this, in association with the mass lesion, can produce a characteristic appearance. Lesions associated with fibrosis tend to produce narrowing, angulation and lack of extensibility as well as characteristic mucosal alterations. In certain cases, such as hypernephroma, in which the desmoplastic reaction is minimal, the tumors tend to be bulky and the roentgen changes reflect this morphology.6

Metastatic lesions may be divided into two groups: (1) colonic involvement by extension from an extracolonic mass, and (2) primarily mural involvement. There is, however, considerable overlap of the two types. The cases illustrated in this report are different patients but have been selected to demonstrate a sequence of events.

COLONIC INVOLVEMENT BY AN EXTRACOLONIC MASS

In this group, there is an orderly sequence of roentgen changes which are best demonstrated in the rectal and sigmoid regions. Initially, the colonic mass (rectal shelf) displaces, stretches and indents the rectum (Fig. 1). With further growth and infiltration, the rectum narrows and its anterior aspect becomes irregular with numerous nodular defects. If the posterior wall of the bowel remains distensible, it arches over the fixed area of involvement (Fig. 2).

In some cases of concentric involvement of the colon, limited extensibility is the predominant feature. The mucosa then assumes a striking appearance with fixed transverse folds of variable length and thickness. In cases of eccentric involvement on the other hand, the folds may radiate toward the site of fixation and maximal involvement (Fig. 3). The appearance of the folds is one of the most distinctive features of this condition. However, the exact cause of the fixation of the folds in a transverse parallel arrangement is not known. It is most likely related to concentric involvement and restricted extensibility of the walls incident to neoplastic invasion. At this stage, there is not only limited distensibility but the bowel cannot completely col-

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Fig. 1. Metastatic carcinoma, primary unknown. There is a mass (rectal shelf) in the pelvis which fixes and compresses the rectum. There are no mucosal changes.

lapse. As mural invasion continues, the transverse folds are replaced by nodular defects and mucosal ulceration may follow

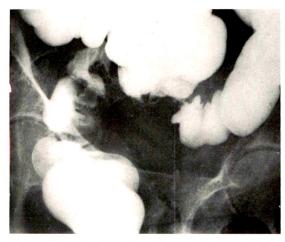


Fig. 2. There is a large irregular mass anterior to the rectum and sigmoid. On the anterior wall, there are multiple nodular defects and limited distensibility and extensibility. Normal lengthening of the posterior uninvolved wall produces "pseudosacculations" and indicates partial involvement of the bowel circumference.

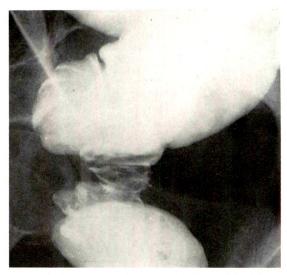


Fig. 3. Metastatic carcinoma, primary stomach. The midportion of the rectum is narrowed. The mucosal folds are transversely fixed and have a crowded appearance due to lack of extensibility as well as limited distensibility. These changes are secondary to circumferential involvement by metastatic carcinoma.

(Fig. 4). In late stages, there is extreme limitation of extensibility and distensibility with marked compromise of the lumen and no recognizable mucosa. The rectum or sigmoid becomes rigid and tube-like (Fig. 5) and finally may be completely obstructed. Other segments of the colon show very similar changes, indentation and displacement (Fig. 6A), fixation and thickening of folds (Fig. 6B; and 7, A and B), ulceration (Fig. 7C), lack of extensibility and distensibility and obstruction (Fig. 8, A, B and C).

MURAL INVOLVEMENT

The lesions may be single or multiple. An isolated metastatic lesion appears as a shallow, broad-based defect without overhanging edges (Fig. 9, \mathcal{A} , \mathcal{B} and \mathcal{C}). The absence of ulceration until the late stages is of diagnostic importance. The contours of the lesion are usually finely or grossly nodular. The mural mass may grow predominantly intraluminally or extend beyond the bowel wall into the mesentery involving adjacent segments of both small and large intestine



Fig. 4. There is a large mass involving the rectum with destruction of the mucosa of the involved segment. At this stage, because the intrinsic process predominates over the extrinsic component, differentiation from a primary carcinoma is not possible.

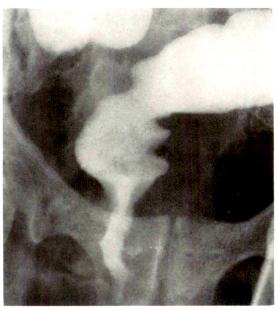


Fig. 5. Extension of prostatic carcinoma into the rectum. The rectum is markedly narrowed with complete effacement of the mucosa. At this stage, differentiation from an inflammatory stenosis may be difficult without additional information.

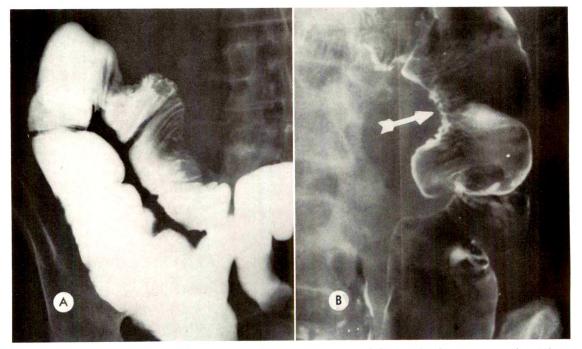


Fig. 6. (A) Two metastatic nodules compress the superior aspect of the proximal transverse colon. Along this contour, the folds are fixed, crowded and stretched transversely. (B) Minimal changes of metastatic carcinoma from the stomach to the colon. There is pleating of the folds associated with a small mesocolic mass (arrow). On the opposite or lateral uninvolved wall, sacculations are seen.

(Fig. 10, A and B; and 11). Circumferential progression narrows the bowel lumen and may lead to obstruction (Fig. 12). Intussusception is rare because of external fixation.

Multiple metastatic nodules may be of varying sizes and show differing stages of mural involvement (Fig. 13). These im-

plants may be tiny and their only roentgen manifestation is fine spiculation along the bowel contours and abnormal contraction of that segment of the colon. Diffusely infiltrating involvement may occur and be associated with marked fibrosis producing an appearance indistinguishable from pri-



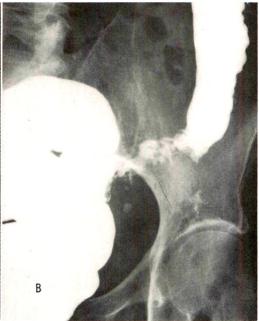




Fig. 7. (A) There are multiple nodular defects along the medial aspect of the sigmoid associated with narrowing of the lumen and limited extensibility. The mural involvement has produced a striking configuration of the folds which are stretched, fixed, transversely arranged and oriented towards the extra colonic mass. This configuration is highly suggestive of metastases. (B) Multiple mucosal implants produce nodularity of the contour of the sigmoid with narrowing of the lumen and distorted mucosa. There is no ulceration. (C) In the distal sigmoid, transverse, fixed folds oriented towards an extracolonic mass are seen. Proximally, the mucosa is ulcerated (white arrow) and there are multiple mural nodules narrowing the lumen. Fixation to the extrinsic mass angulates the sigmoid and flattens the cecum (black arrow). This case demonstrates the three types of involvement, namely, an extrinsic mass, mural and mucosal involvement.

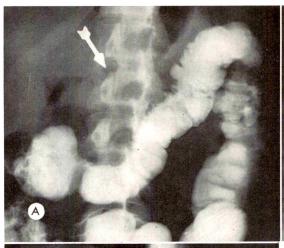
mary scirrhous carcinoma of the colon. This type of involvement is most often seen with metastases from breast carcinoma.¹¹

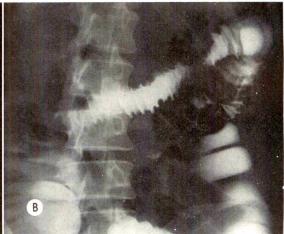
Metastatic hypernephromas present a special situation. Because of minimal desmoplastic reaction, large bulky cellular tumors occur. These tumors, originating outside the bowel, grow rapidly through the wall and produce large intraluminal masses (Fig. 14). The salient roentgen features in distinguishing these metastases are their large sausage-like intraluminal components which may or may not ulcerate. These have no tendency to become circumferential, do

not angulate or contract the bowel and as a result rarely lead to obstruction.

DIFFERENTIAL DIAGNOSIS

A solitary metastatic nodule, though difficult to differentiate from primary carcinoma, nevertheless may present distinctive features. These relate largely to its submucosal location and consist of: (a) a broad-based contour defect, (b) an obtuse angle between the margin of the defect and normal bowel, (c) frequently an associated extrinsic mass, (d) fixation of the mucosal folds in the vicinity of such nodules, and (e) most important, the absence of mucosal





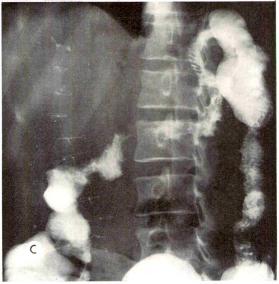


Fig. 8. (A) The mesocolic aspect of the transverse colon involved by carcinoma of stomach is fixed and shows limited extensibility. Extrinsic fixation has produced arching of the bowel. The normal haustral pattern is absent. There is a soft tissue defect within the air column in the stomach (arrow). (B) More marked involvement of the transverse colon. The transverse, thick, fixed folds are the result of lack of extensibility and distensibility occasioned by circumferential intramural involvement by carcinoma. Nodular defects narrow the lumen. (C) Extensive irregular narrowing is present throughout the colon. Maximum involvement occurs in the midtransverse colon adjacent to the stomach. The mucosal pattern is distorted in all areas to different degrees.

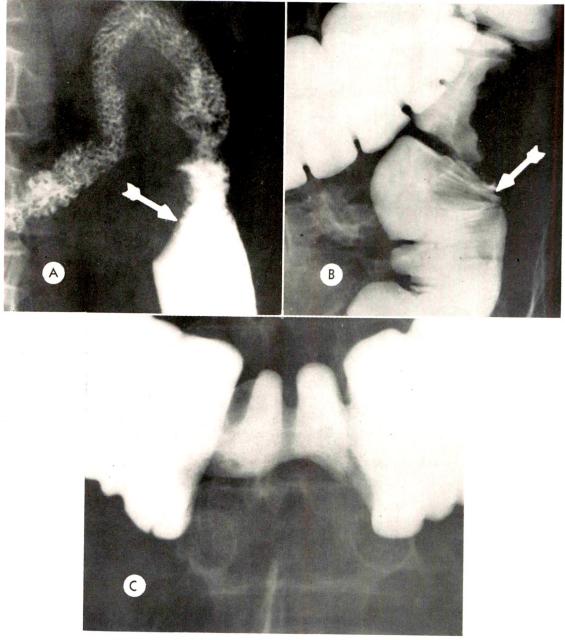


Fig. 9. (A) There is a shallow extramucosal mass in the proximal descending colon produced by a solitary metastatic nodule from the ovary (arrow). The mucosa is intact. (B) Another patient with more extensive involvement. The appearance at this stage is still that of a submucosal lesion as evidenced by a shallow, broad-based, filling defect without overhanging edges. Irregularity of the mucosa indicates that involvement of this layer has occurred. Pleating of the folds at the lower edge suggests an extracolonic mass (arrow). (C) Large metastatic lesion from carcinoma of the pancreas. The shallow defect in the transverse colon still resembles an extramucosal lesion. However, because of the steep margins and mucosal ulcerations, primary carcinoma also must be considered.

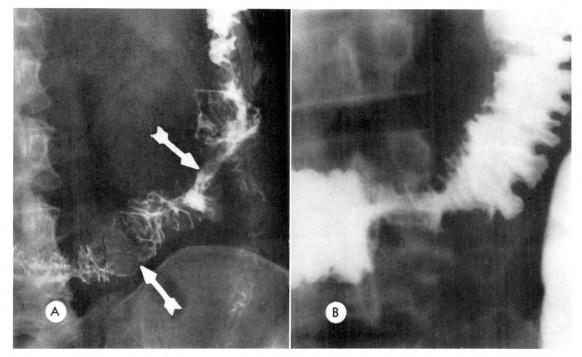


Fig. 10. (A) A primary carcinoma of the distal transverse colon is present (upper arrow). Immediately proximally, there is an intramural metastasis which stretches and distorts the mucosa (lower arrow). There is no ulceration. At operation, the mucosa was intact. The metastasis was distinct from the primary. (B) Extramucosal involvement of the transverse colon by metastatic carcinoma of the lung. The mucosal folds are thickened and fixed but not ulcerated. Extramucosal discrete nodules on the inferior border produce eccentric narrowing of the colon.



ulceration. All these characteristics must be present to warrant a diagnosis of metastasis. The detection of other nodules having similar characteristics reinforces the suspicion of metastases. When the lesion ulcerates or becomes circumferential, differentiation from a primary carcinoma may be impossible.

Differentiation from submucosal tumors, of which lipoma is the most common, is rarely a problem. The lipoma has smooth

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Fig. 11. In this case, the metastatic lesion from the lung has encircled the descending colon causing narrowing of the lumen and mucosal ulceration simulating a primary carcinoma (arrow). A large extrinsic mass involves not only the splenic flexure but the transverse colon as well.

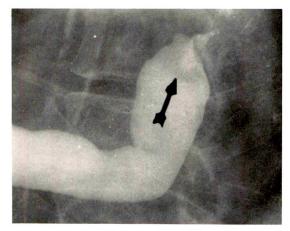


Fig. 12. Complete obstruction of the distal transverse colon by circumferential metastatic lesion from cecal carcinoma demonstrated by barium introduced through a diverting colostomy. There is no overhanging edge and at operation the mucosa was not ulcerated. The proximal margin of the intraluminal component is indicated by an arrow.

contours, is usually intraluminal and has a varying configuration.

In lymphosarcoma of the colon, the submucosal nodules are associated with multiple intraluminal polypoid defects and thickened folds. The colon is dilated rather than narrowed. In the rare situation in which lymphosarcoma presents solely as intramural defects, differentiation from metastases can be difficult. The presence of fixed folds oriented towards an irregular nodule and angulation of the involved segment of colon differentiate metastatic lesions from this form of lymphosarcoma.

Endometriosis can completely mimic a metastatic nodule. In most cases of endometriosis, the lesion has been single rather than multiple. Only a characteristic clinical story may provide the diagnosis.

Granulomatous colitis, because of its obvious mucosal changes, is rarely a problem in differential diagnosis. In an occasional case of granulomatous colitis, discrete nodules along the contour dominate the findings and the resemblance to metastatic carcinoma is more marked. In metastatic carcinoma, however, the metastatic nodules are more irregular, the colonic wall

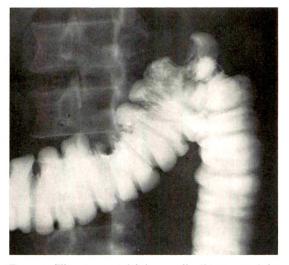


Fig. 13. There are multiple, small, discrete nodules at the superior aspect of the distal transverse colon. The mucosa is intact but distorted and fixed.

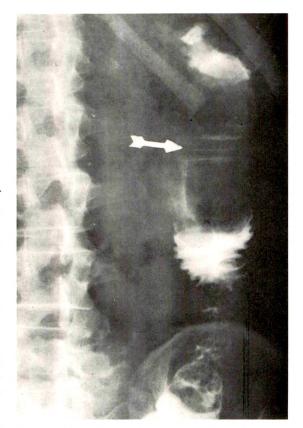


Fig. 14. Extension of recurrent renal carcinoma to the descending colon. A large, lobulated, sausage-shaped, intramural mass widens the lumen of the descending colon. The overlying mucosa is fixed in stretched, transverse, parallel folds (arrow).

more rigid and the fold pattern adjacent to the nodules fixed. Extracolonic masses and angulation of bowel favor the diagnosis of metastatic disease.

Ulcerative colitis, particularly involving the rectum, may have an appearance identical to the late stages of metastatic involvement. A similar appearance may be produced by lymphopathia venereum. Sigmoidoscopy, biopsy and a Frei test help in differential diagnosis.

SUMMARY

The roentgen features of metastatic disease to the colon may be diagnostic and have been divided into 2 groups: (1) colonic involvement by extension from an extracolonic mass and (2) primarily intramural involvement.

The more common roentgen findings include narrowing of the lumen, obstruction, nodular defects, fixed transverse or radiating folds, limitation of distensibility and extensibility and incomplete collapsibility. Ulceration is absent until the late stages. Diffusely infiltrating involvement may occur and be associated with marked fibrosis, producing an appearance indistinguishable from primary scirrhous carcinoma of the colon. Metastatic hypernephromas, because of minimal desmoplastic reaction, produce large bulky cellular tumors.

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THE ROENTGEN APPEARANCE OF INTESTINAL AMEBIASIS

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THE diagnosis and the therapy of amebiasis remain difficult and complex, despite knowledge since 1875²⁶ of the causative organism, *Entamoeba histolytica*. The roentgen features of intestinal amebiasis were first described by Vallarino³⁹ in 1925, but the role of the radiologist has often been overlooked. The purpose of the author is to re-emphasize the value of the roentgenographic examination in the diagnosis and management of intestinal amebiasis.

GENERAL CLINICAL CONSIDERATIONS

Amebiasis encompasses all human infections caused by the protozoon *Entamoeba histolytica*. Man is invaded by the ingestion of viable cysts. This usually results from fecal contamination of food or drink. The walls of the cysts disintegrate in the alkaline small intestine, releasing the motile trophozoites. The trophozoites pass into the colon, where they invade the mucosa.

The majority of people infested with *E. histolytica* are asymptomatic carriers, with the organism a harmless commensal protozoon in the wall of the colon. The cases of amebic disease are divided into 2 forms: (1) acute amebic dysentery, and (2) chronic amebic colitis or amebic granuloma.

Less than 10 per cent of the patients with proved amebiasis demonstrate the acute picture of amebic dysentery. These patients have acute, severe diarrhea with blood and mucus in the stools. They also exhibit marked systemic malaise and toxemia. Their attacks resemble acute idiopathic ulcerative colitis and may be fulminating, and even fatal. In the United States such cases are occasionally seen in local epidemics, especially in institutionalized populations, such as in mental hospitals and prisons.

Usually, the course of intestinal ame-

biasis is slow and insidious. The symptoms and signs are often nonspecific, and they manifest themselves many years after exposure. The patient may have attacks of mild diarrhea, or diarrhea alternating with constipation, or just constipation. Crampy lower abdominal or right lower quadrant abdominal pains are often present. Fever is not common and, when noted, is usually low-grade. The patient may emphasize vague symptoms, such as fatigue, anorexia, or various aches. In the more severe amebic attacks, moderate diarrhea, often bloodtinged, is characteristically present; a mass may be palpable.

Extra-intestinal amebiasis is secondary to bowel infection; the most common site is the liver. Trophozoites are carried from intestinal radicles via the portal venous system, usually producing a single liver abscess. Radioactive isotope scanning has proved to be of great value in the detection and in the serial follow-up of amebic abscess of the liver (Fig. 1). In some cases, hepatitis or multiple abscesses are seen. Pulmonary amebiasis is second most common and is usually due to direct, transdiaphragmatic extension from an hepatic abscess. Occasionally, there is hematogenous spread to the lungs, with or without liver disease.

The definitive diagnosis of amebiasis depends on the laboratory recognition of the organism. The trophozoites are usually present in the diarrheal stools, but the cysts are more frequently found in formed stools since their dry conditions favor encystation. It is generally recommended that at least 6 fresh, warm stool specimens be examined when searching for amebiasis. Brooke⁴ has recently restated the laboratory deficiencies in the United States. Both the training and the experience of the laboratory technician are frequently inade-

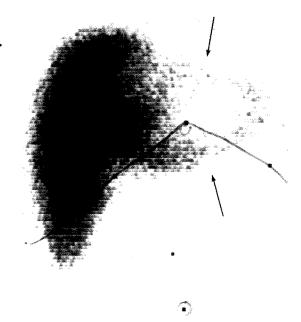


Fig. 7. Colloidal gold Au¹⁹⁸ hepatic scan showing a large amebic abscess (arrows) in the left lobe of the liver.

quate in the diagnosis of amoebae in the stool; amoebae are not found when they are present and false-positive diagnoses are often made.

Because of the laboratory problems, the sigmoidoscopic examination, with smear and biopsy, is vital, but is often neglected. Although the proctoscopic appearance may be suggestive of amebiasis, biopsy is essential. Brown and Winkelman⁵ recently reported 12 cases with typical clinical and proctoscopic findings of idiopathic ulcerative colitis, which were later proved to be caused by amebiasis. In the more endemic area of Greece, Doxiades and Yiotas¹² have doubled their diagnostic accuracy by the addition of a routine rectal biopsy to the laboratory study of stool specimens. In most of their cases of amebiasis, mucosal ulcerations or other abnormalities were evident, but in other cases blind biopsy of grossly normal mucosa revealed the amoebae.

The United States prevalence rate of amebiasis has been frequently studied and has been cited as high as 10 to 20 per cent, but is more likely about 5 per cent.^{4,28} The

rate is higher in rural areas and in lower socio-economic groups, reflecting poor sanitary conditions which allow fecal contamination of food and water. (Amebiasis is transmitted from man to man; there are no intermediate hosts.) In the tropics, where sanitation is often poor or nonexistent, amebiasis is a widespread disease.

PATHOLOGIC CONSIDERATIONS

The amoebae invade the mucosa, producing small, papillary areas of inflammation, which rapidly undergo superficial necrosis to form ulcers. Thus, the usual early gross appearance is of multiple discrete ulcerations or erosions, with normal intervening mucosa. In some early cases, ulcerations are not present; the mucosa exhibits only diffuse hyperemia and friability. Some early ulcers may be pinhead in size, with a ring of surrounding erythema; others are small and shallow, with raised margins, containing mucus and necrotic material. These ulcers often involve only the mucosa, but after their growth and coalescence they form larger, more characteristic ulcers which involve the submucosa as well as the mucosa. These are the classic, deep "flask-shaped" ulcers, with undermined, or overhanging, shaggy edges.

In his classic paper, Lasnier²⁴ described 3 zones of different histologic structure in the characteristic amebic lesion. The inner or surface zone was composed of necrotic tissue containing red and white cells, fibrin and colonies of E. histolytica. The middle zone was formed principally of chronic inflammatory cells and granulation tissue. The external laver was an area of fibroblastic reaction and was completely fibrous in its outermost part. It is generally believed that involvement of the muscularis or beyond cannot occur without secondary bacterial infection. Thus, the basic pathologic process is a granulomatous thickening of the colon, resulting from an ulcerative necrosis by the amoebae, from secondary bacterial infection, and from the reaction

The amebic disease may involve exten-

sive areas of the colon or may form a welllocalized lesion, sometimes called an amebic granuloma or "amoeboma." The distribution of the colon lesions was first emphasized by Clark,10 and has since been repeatedly confirmed. About 90 per cent of patients with chronic amebic colitis have cecal involvement. Ascending colon disease is not uncommon, but almost always continuous with cecal disease, and is difficult to evaluate statistically. Next to the cecum, n order of frequency of involvement, are the rectum, the sigmoid colon, and the transverse colon. Rectal disease is often continuous with sigmoid involvement. Segmental, skip lesions with intermediate normal areas are present in 30 to 40 per cent of cases.

The small intestine is very rarely involved by amebiasis. Clark¹⁰ found no small bowel disease in 186 necropsy cases. Delahaye *et al.*¹¹ found no ileal abnormalities in a roentgenologic study of 171 cases of chronic intestinal amebiasis. The rare cases of ileal disease are noted mainly in patients with severe, rapid fulminating disease, often of the entire colon.^{22,37}

Complications of amebiasis of the colon are rare in the subacute or chronic stages of the disease. Because of the great thickening of the bowel wall caused by the amebic process, perforation, either into the peritoneal cavity or locally with abscess formation, is very uncommon. Similarly, fistulae and sinus tracts are rare. In a recent report of 2 unusual cases of enterocolic amebic fistulae,36 the barium enema failed to fill the fistula in either case. Complete obstruction, even with a well-localized lesion, is extremely rare. Severe hemorrhage is generally seen only in the occasional, fulminating cases of diffuse amebic dysentery. In these cases, death may occur from the severe general toxicity or from perforation, producing diffuse peritonitis.22

ROENTGENOLOGIC CONSIDERATIONS

The roentgen findings of amebiasis reflect the pathologic processes of ulceration, inflammation, and fibrosis. The individual ulcers are usually too shallow to be detected roentgenologically. But in the early stages, before much reactive bowel change, the multiple ulcerations over a length of bowel often create an abnormal mucosal appearance. The margins or contours of the bowel may have minimal irregularity (Fig. 2A), or even serration or "saw-toothing." En face, the mucosal pattern may be granular or even mildly pseudopolypoid (Fig. 5B). It has been stated, however, that by themselves these mild mucosal alterations are difficult to interpret.¹¹ They may be noted only on postevacuation or air contrast roentgenograms.

The inflammatory response produces the roentgen manifestations of (1) spasm and irritability, (2) narrowing of the lumen or lack of distensibility, and (3) deformity of the haustral pattern and of the bowel margins. Spasm manifests itself fluoroscopically by an intermittent or variable, concentric, segmental area of narrowing. Often the degree that spasm contributes to colon narrowing and deformity is evident only in retrospect, when repeat or early follow-up examinations show an overly rapid improvement. Lack of distensibility and narrowing of the lumen are the most common roentgen findings (Fig. 6, A and B). The inflammatory thickening of the wall of the colon is not demonstrable on the barium enema roentgenograms, but causes narrowing of the lumen. The haustral change is usually seen as either an exaggeration or an irregularity of the haustral pattern¹¹ (Fig. 3A and 6A). The frequent deformity of the bowel margins results from the same factors that cause narrowing: spasm and inflammatory thickening.

As fibrosis increases, one sees the development of shortening and narrowing of the involved colon. The "contracted cecum" or "coned cecum" is the classic and most frequent picture of this later stage of amebic colitis (Fig. 3B and 5C). The margins of the bowel may still be irregular, because of persistent chronic inflammation. The fibrous element is not easily separated

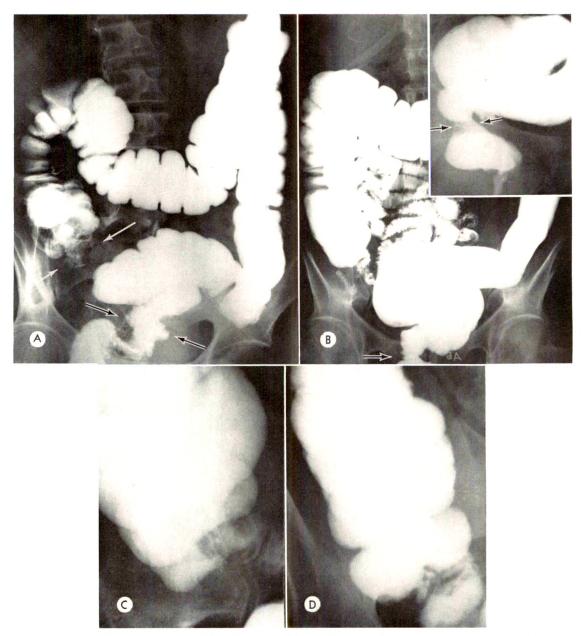


Fig. 2. A 52 year old man was admitted with a 1 week history of crampy lower abdominal pain, diarrhea, fever and chills. Sigmoidoscopy disclosed a firm, polypoid mass at 10 cm., and multiple superficial mucosal ulcerations throughout the distal 13 cm. (A) Barium enema examination shows severe contraction of the cecum (white arrows); there is no reflux into the terminal ileum. Mild irregularity, suggestive of ulceration, is diffusely present throughout the rectosigmoid colon (black arrows). (B) Re-examination after 3 weeks of anti-amebic therapy shows no essential change in the cecum; the terminal ileum and appendix are normally filled. In the rectosigmoid colon the diffuse lesions are gone, but a smooth, short stricture is evident (arrows). (C and D) Roentgenograms of the cecum at the time of the study shown in (B) and at a 2 year follow-up. The contraction of the cecum has diminished, but there is still slight residual deformity.

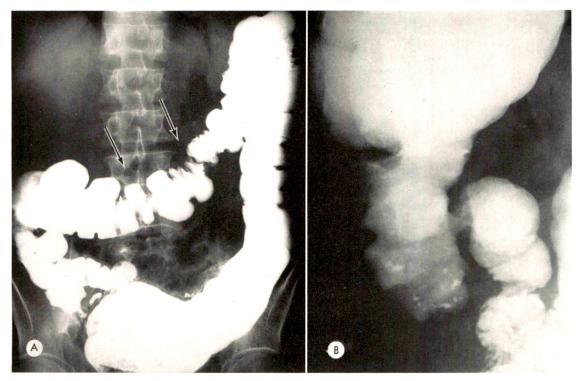


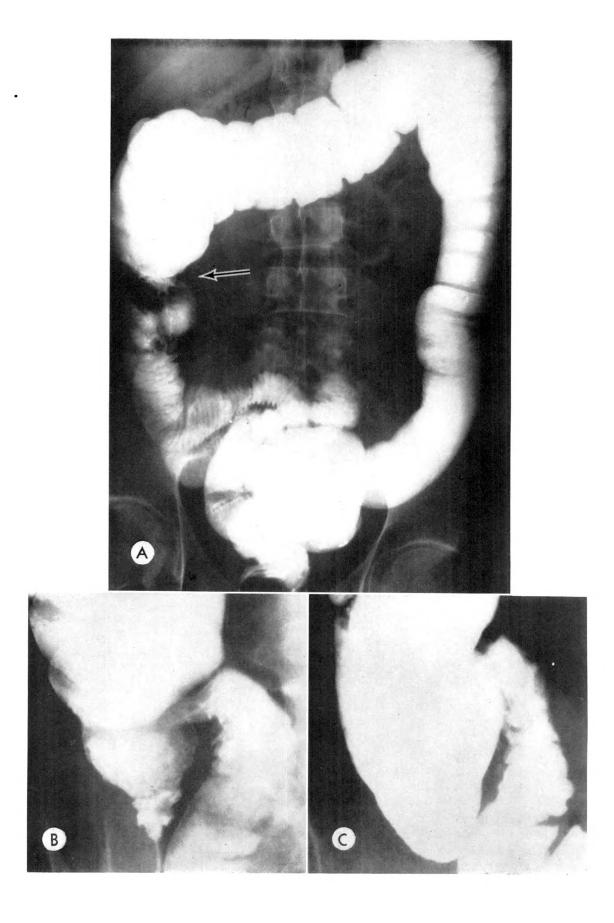
Fig. 3. A 58 year old man was admitted with a 2 week history of lower abdominal pain, diarrhea and fever. A tender right lower quadrant abdominal mass was palpated, suggesting an appendiceal abscess. (A) Deformity of the cecum is visualized, as well as irregularity of the haustral pattern (arrows) of the transverse colon. (An area of rectosigmoid irregularity was also present.) (B) Cecal constriction and contraction are better demonstrated; the terminal ileum is normal.

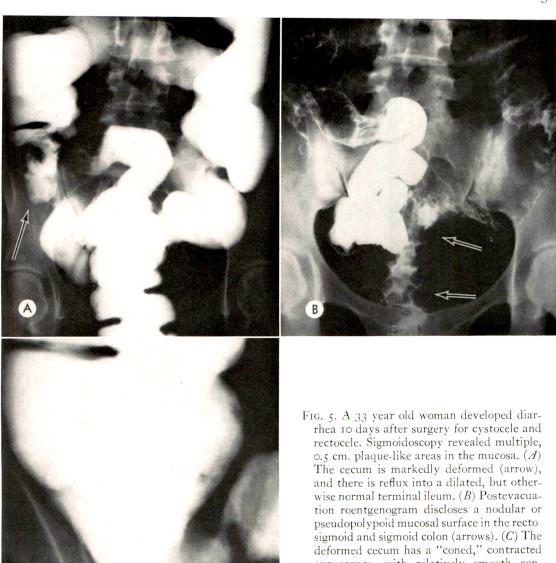
from the rest of the inflammatory reaction, except when serial studies during therapy show a stable, contracted lesion. Therapy often produces a healing that rapidly returns the bowel architecture to an almost normal appearance (Fig. 4, A, B and C). Much of the severe deformity and narrowing is caused by spasm and reversible inflammation, but occasionally severe scarring produces significant permanent deformity. In such cases, the cecum remains contracted, or the distal colon forms a smooth, well-localized stricture (Fig. 2, A–D).

As previously stated, ileal involvement in chronic amebiasis is almost unknown. Certainly, it is agreed that a small bowel series should be done whenever inflammatory disease of the colon is found.⁴⁴ During the barium enema, the ileocecal valve is usually incompetent, often producing

striking reflux into the ileum. However, this finding is not always present, and in some cases no ileal filling can be achieved (Fig. 2A).

Occasionally, the granulomatous inflammatory response may be so severe and so localized that a palpable, tumor-like mass, or amoeboma, is present. In these cases, long-standing chronic ulceration and inflammation have produced considerable thickening and deformity of the bowel walls in a circumscribed area. 16,24 In only a few of these cases, however, is the bowel lumen so abnormal that a carcinoma is suggested. In almost all of the roentgen pictures of amebiasis, the inflammatory characteristics clearly predominate. The length of the lesion is greater than in cases of carcinoma. Its margins have tapered or gradual transitions to the adjacent normal bowel. Gross mucosal destruction and





appearance, with relatively smooth contours.

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F16. 4. A 28 year old man had episodes of crampy abdominal pain and mild diarrhea for 2 years. (A) Severe contraction of the cecum (arrow) is present, with free reflux into a normal terminal ileum. (Diffuse, tiny ulcerations of the rectum and rectosigmoid colon could not be easily reproduced.) (B and C) Roentgenograms of the cecum before and after 3 weeks of anti-amebic therapy, showing its return to an almost normal appearance.

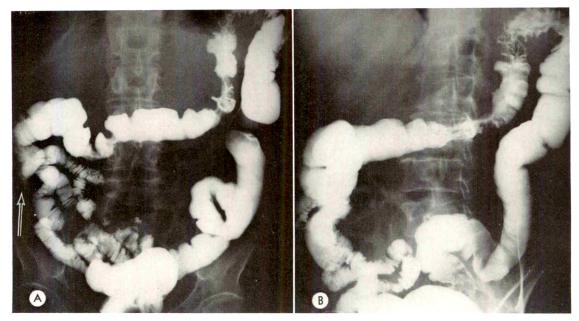


Fig. 6. A 68 year old man complained of right-sided abdominal pain of 3 months' duration, accompanied by a 15 pound weight loss. The patient underwent exploratory surgery and partial colon resection, and died postoperatively. (A and B) Frontal and oblique roentgenograms reveal contraction and shortening of the cecum (arrow) and ascending colon. There is a lengthy skip area of involvement in the transverse colon (including the splenic flexure) with narrowing and irregularity. (Courtesy of George J. Meyer, M.D., Fort Lauderdale, Florida.)

rigidity of the bowel wall are not present. Complete, or even severe, colon obstruction is extremely rare.

Since the roentgen findings of ulceration, inflammation, and fibrosis are common to multiple inflammatory diseases of the colon, one must understand that there are no specific roentgen abnormalities and that it is important to consider the localization and the extent of the disease. Findings that suggest amebic colitis are: (1) a concentric, inflammatory involvement of only the cecum; (2) a cecal inflammation with a skip area of disease in another segment of the bowel, especially the rectum or the rectosigmoid region; and (3) a normal terminal ileum. In the subacute or chronic cases, there is rarely diffuse involvement of the entire colon or even of the entire left half of the colon.

DIFFERENTIAL DIAGNOSIS

Carcinoma of the colon is not infrequently a major clinical consideration, but

as previously discussed the roentgenographic picture of amebic disease of the colon is almost always clearly inflammatory. Occasionally, severe cecal lesions present a problem. Cecal carcinoma, however, is usually an asymmetric filling defect, with a markedly irregular or polypoid contour, while the amebic cecum exhibits symmetric or concentric narrowing, with more regular margins and no rigidity.

In cases of metastatic carcinoma to the bowel, short lesions are usually present, unlike amebiasis. Metastases may be either single or multiple; eccentric or annular. Occasionally, however, a long portion of the colon may be enclosed in a sheath of metastatic carcinoma. Such an area may have limited distensibility, gradual margins, and some intact mucosal folds, and may thus resemble inflammatory disease. 42

It has been pointed out in the past⁴⁰ that inflammatory disease of the colon produces similar roentgen findings because of the common inflammatory changes of ulcera-

tion, mural thickening, and bowel shortening and narrowing. The emphasis remains paramount in the radiologist's interpretation on distinguishing between neoplastic and non-neoplastic lesions of the colon, ⁴¹ but a review of other inflammatory conditions of the colon will raise some helpful differential features. Because of the common localization of amebiasis in the cecum, the differential diagnosis should include dis-

eases that are prominent in this area of the

colon.

- 1. Crohn's disease or granulomatous colitis. This disease is the leading consideration in the differential diagnosis of amebic colitis. In approximately 80 per cent of cases of Crohn's disease involving the colon, however, there is simultaneous involvement of the ileum.²¹ In those cases of Crohn's disease only in the colon, there is often diffuse or almost diffuse disease in the entire colon,²⁵ unlike chronic amebiasis. When Crohn's disease presents as only single or multiple localized areas of abnormality in the colon, one may note differential roentgen features (not present in amebiasis) such as longitudinal and transverse ulcers and fissures, a "cobble-stone" mucosal pattern, eccentricity of involvement, and fistulae.44 It should be noted that Rudhe and Keats's early sign³¹ of exaggeration of the haustral pattern in Crohn's disease is often present in amebiasis.11
- 2. Diverticulitis, especially in the cecum,³⁴ presents as an eccentric, intramural indentation or filling defect. There is no symmetric, concentric spasm or contraction of the cecum as in amebiasis. The contour of the bowel is less irregular than in amebiasis because of lack of mucosal disease. Often diverticula are seen near the area of active disease.
- 3. Idiopathic ulcerative colitis produces diffuse, uniform, continuous involvement of a great length of the colon, often with generalized shortening of the bowel. Segmental inflammatory areas, especially skip lesions, are rare. Ileal disease may be seen, especially in right-sided ulcerative colitis.

However, in the occasional cases of acute, diffuse amebic dysentery of the entire colon, the roentgen picture is probably indistinguishable from ulcerative colitis.¹³

- 4. Tuberculosis. The cecum is the most common site of colon disease and there may be skip areas of involvement, as in amebiasis.³ About 85 per cent of cases of colon tuberculosis have disease of the terminal ileum.⁶ This is the only differential roentgen feature of value. Stierlin's sign, caused by marked irritability of the cecum, is a nonspecific inflammatory finding. In occasional cases of solitary cecal disease, one relies on other clinical and laboratory data, including the chest roentgenogram.
- 5. Appendicitis or appendiceal abscess. An extrinsic pressure defect is seen, usually well-localized to the base of the cecum. The defect is relatively smooth, since there is little or no mucosal involvement. If present in the usual location of the appendix, an eccentric, extrinsic compression of the terminal ileum may also be visualized. A coprolith may be seen; this may also occur in diverticulitis of the colon. Foreign body perforation of the cecum, like appendiceal abscess, appears mainly as a pericolic abscess.
- 6. Schistosomiasis. In this granulomatous inflammation, disease is usually confined to the left colon and involvement of the cecum and ascending colon is rare. The rectosigmoid is first and the descending colon second in frequency of involvement. The roentgen features are similar to amebiasis, except for the frequent finding of prominent, inflammatory polyposis. Stool examination, or biopsy of the rectum or liver, is definitive.
- 7. Actinomycosis is a rare disease of the colon. The appendix is the most common site of actinomycosis in the intestinal tract. A granulomatous abscess or mass is formed, usually spreading extensively, often to the retroperitoneum. There are multiple draining fistulae, especially to the skin of the anterior abdominal wall, as seen in all 16 cases of actinomycosis of the appendix and colon reported by Harvey et al.¹⁷

8. Vascular and hemorrhagic disease of the colon. The diagnosis of these diseases is suggested by the clinical history. Ischemic disease is usually in the left colon and produces multiple pseudotumors ("thumb-printing").³⁵ Intramural hematoma produces either uniform, regular thickening of the folds or "thumb-printing."²³ In some cases, especially of ischemic disease, ulceration, edema and spasm present findings resembling a colitis. The cardinal feature is rapid change, without therapy, on serial studies within 1 to 2 weeks.³⁵

DISCUSSION

It is important to re-emphasize the role of the radiologist in amebic disease of the colon. There is continual discussion of the disease in the nonradiologic American literature, while no direct comment has appeared in the American radiologic literature in almost 20 years. ¹⁹ Meanwhile, radiologists have become more interested in segmental, non-neoplastic colon lesions, especially Crohn's disease. The presence of significant roentgen abnormalities in many cases of amebic colitis places this disease in the radiologist's realm.

Vallarino.³⁹ in 1925, was one of the earliest authors to stress the value of the roentgenogram in amebiasis of the large intestine. He pointed out that the roentgen study was able to determine the location, extent, and severity of the disease, and the response of the lesions in the course of treatment. In the following decade, both Bell^{1,2} and Ikeda²⁰ enlarged the role of the radiologist by depicting the common cecal findings and by showing that in some cases the possibility of amebiasis was first considered only after roentgen examination. Wilbur and Camp⁴³ also showed that the radiologist often was the first to suspect the diagnosis of amebiasis. Golden and Ducharme¹⁵ found cecal deformity in 30 of 32 roentgenologic cases and stated that the roentgenogram alone is sufficient to suggest the diagnosis.

Because of the present awareness of Crohn's disease of the colon, it is pertinent

to state that all of our 5 illustrated cases of amebiasis have skip areas of disease. There has been insufficient attention paid in the radiologic literature on amebiasis to the combination of rectosigmoid or other skip lesions with the oft-quoted cecal deformity. In contrast, the importance of rectal biopsy has been stressed in recent years by the gastroenterologists. 12,27

The radiologist's role is underscored by the tendency to surgically explore a segmental lesion of the colon for suspicion of carcinoma. In their extensive clinical review, Spicknall and Peirce³⁸ demonstrated the high surgical mortality rate in colonic amebiasis and reaffirmed Hawe's 18 surgical experience that "... there are few exceptions to the rule that operation is strongly contraindicated in intestinal amebiasis." It has often been warned that negative stools do not exclude amebiasis and that positive stools do not prove that the patient's symptoms are caused by the amoebae. Thus, unnecessary and dangerous surgery will be averted when the barium enema roentgenogram is carefully studied for the possibility of amebiasis.

The term amoeboma29 or amebic granuloma¹⁶ has been repeatedly used in the literature. It is probably of little value since its clinical definition depends on the palpability of a mass. This term has exaggerated the clinical resemblance of some cases of amebiasis to carcinoma and has obscured the role of the radiologist in excluding neoplasm. In the occasional difficult case, it is important to await the roentgen and clinical response of the disease to specific anti-amebic therapy. Almost all amebic lesions, including amoebomas, show rapid and dramatic improvement, and often completely disappear, within I month.32,33,38

The surgical implications of amebiasis of the colon have been reviewed by Ochsner and De Bakey²⁹, who also warned of the dangers of exacerbating the disease or perforating the colon by unprepared surgical intervention. Amebiasis may present the clinical picture of an appendiceal abscess;

in most of these patients there is only cecal disease, but occasionally there is simultaneous amebic involvement of the appendix. The place for surgery is in the occasional well-localized lesion, where chemotherapeutic control of the disease has resulted in an irreversible, significant area of fibrous narrowing or stricture.

In amebic colitis, the percentage of roentgenologically positive studies depends upon the severity of the disease. Reflecting the extensive New Orleans experience, Browne et al.7 feel that approximately 70 per cent of patients with acute disease and approximately 40 per cent with chronic disease have roentgenologic changes. Patients who are asymptomatic carriers or who are mildly asymptomatic usually have normal examinations. Golden and Ducharme15 found that the majority of the patients with diarrhea as a chief complaint have abnormal barium enema studies. Cecal irritability has been mentioned as the earliest roentgen sign of disease, but a cecal deformity which is not persistent is probably not significant.15

There are acute, fulminating cases of amebic dysentery, where the radiologist has little or no role.33 These cases have diffuse involvement of the entire colon, which clinically and roentgenologically resembles idiopathic ulcerative colitis or bacillary dysentery.5,13 Even toxic dilatation of the colon has been described in this form of amebic colitis.⁵ Smart,³⁷ however, recently described 3 cases of acute amebic dysentery and felt that the roentgenologic changes were atypical of ulcerative colitis. He stressed that his cases had unusual and severe mucosal irregularity and had areas of both narrowing and dilatation. In these infrequent, fulminating cases, laboratory examination of stool or biopsy material readily furnishes the diagnosis, and even Smart³⁷ states that the barium enema examination may be dangerous as the friable colon is liable to perforate.

CONCLUSIONS

1. The radiologist has a valuable role in

the diagnosis and treatment of intestinal amebiasis.

- 2. The barium enema examination findings alone may suggest the diagnosis.
- 3. The roentgen picture is clearly inflammatory; skip lesions may be an important feature. In general, carcinoma is easily excluded roentgenographically.
- 4. The barium enema examination is helpful in the management of the disease, by determining the location, the extent, and the severity of the lesions.
- 5. The barium enema examination is also helpful in following the response of proven cases to anti-amebic therapy.
- 6. In questionable cases of amebiasis, roentgenographic follow-up during therapy may lead to a conclusive diagnosis.

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SIGMOIDO-ILEAL FISTULAS AS A COMPLICATION OF DIVERTICULITIS*

By PAUL M. KROENING, M.D. TEMPLE, TEXAS

A SIGMOIDO-ILEAL (enterocolic, ileocolic) fistula is an unusual complication of diverticulitis of the colon. The following is a case report concerning a pair of fistulous tracts connecting an area of diverticulitis in the sigmoid colon to a normal segment of ileum. The condition was discovered during a roentgenologic procedure.

REPORT OF A CASE

A 63 year old Mexican woman was admitted to the Scott and White Memorial Hospital in February, 1964 complaining of intermittent abdominal cramping. In March, 1962, she first developed the abdominal pain which was accompanied by bowel tenesmus and hematochezia. Although bed rest relieved her symptoms, a colon examination performed 2 weeks later reportedly demonstrated diverticulosis. At this hospital, roentgenologic examination of the colon demonstrated diverticulosis with leakage of a small amount of barium into the tissues immediately adjacent to the sigmoid, apparently through a small perforation in an inflamed diverticulum (Fig. 1). The patient refused surgical treatment and became asymptomatic with conservative medical management. Subsequently, a proctoscopic examination was performed and the results were negative.

When acute lower abdominal distress recurred in September, 1965, the patient was readmitted to the hospital. A proctoscopic examination revealed shallow mucosal ulcerations in the rectum and lower sigmoid colon. A roentgenologic study of the colon followed, and the barium was noted to pass from an area of deformity in the mid-sigmoid through 2 fistulous tracts into a normal segment of ileum (Fig. 2, A, B and C). The roentgenographic diagnosis was acute diverticulitis with sigmoidoileal fistulas.

The patient's abdomen was explored, and

the sigmoid colon was found to be grossly involved with diverticulitis. A sinus tract connected a diseased segment to normal ileum. Other abnormalities of the intestinal tract were not observed. A fistulectomy and a partial left colectomy were performed. The surgical impression was chronic diverticulitis with an ileocolic fistula.

When the surgical specimen was evaluated morphologically, a segment of sigmoid colon (25 cm. long) was found to contain multiple diverticula. Many of the diverticula were located in an isolated area of diffuse thickening and scarring, and they were unusually elongated. One contained a fecalith which measured



Fig. 1. Evacuation roentgenogram (February, 1964) showing extensive diverticulosis. Note the faint vertical, extraluminal collection of barium adjacent to the mid-sigmoid colon (arrow), which denotes the site of perforation.

^{*} From the Department of Radiology and Radioactive Isotopes, Scott and White Clinic, Temple, Texas.

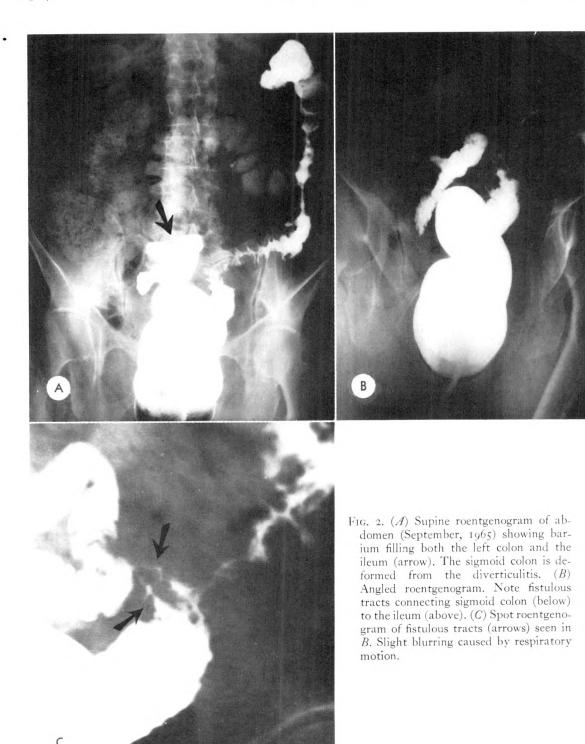




Fig. 3. Surgical specimen of sigmoid colon. The sutures locate the area of perforation and the origin of the fistulous tracts (arrow).

1×0.5×0.5 cm. Two fistulous tracts arose from this area (Fig. 3). Normal ileal mucosa was attached to one end of the fistulas. The mucosa of the sigmoid colon contained islands of diffuse lymphoid hyperplasia with overlying superficial ulceration. Parasites were not present in either fresh smears taken from the bases of these ulcers or in the fixed sections. The pathologic diagnoses were: (1) diverticulosis of the colon with chronic diverticulitis and fistulous connection to the ileum; and (2) nonspecific mucosal ulcerations of the sigmoid colon.

DISCUSSION

Diverticulosis of the colon has an incidence of about 20 per cent in adults. The condition is unusual in children, but it occurs with increasing frequency as age advances.⁴ Diverticulitis, acute or chronic inflammation of diverticula, occurs in about 5 per cent of the patients who have diverticulosis. The usual complications of diverticulitis are perforation, intestinal obstruction, abscess formation, generalized peritonitis, and fistulas.² About 10 per cent of the patients with diverticulitis develop fistulas which usually are of the sigmoidovesico, rectovesico, sigmoido-uterine, sig-

moido-vaginal, anal, and external type. Most uncommon is the sigmoido-ileal fistula.^{1,3}

In this patient, the diverticulitis was of 3 years' duration and a perforation was present for more than I year (Fig. I). To suspect that the superficial mucosal ulcerations which appeared in the later stages of the disease contributed to the development of the sigmoido-ileal fistulas is not tenable. The ulcerations probably resulted from chronic infection. Ulcerative colitis, regional enteritis, or parasitic infestation was not present.

SUMMARY

A case of sigmoido-ileal fistulas (enterocolic, ileocolic) as an unusual complication of diverticulitis of the colon is described. The condition was discovered during routine barium enema roentgenologic examination

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PERFORATION OF THE RECTOSIGMOID BY A BARDEX BALLOON CATHETER

REPORT OF 3 CASES

By RICHARD J. NOVEROSKE, M.D. PRINCETON, INDIANA

IN THE author's experience, the rectosigmoid portion of a normal colon was perforated in a case while a Bardex balloon rectal catheter was being inflated for a barium enema examination. Two other cases of perforation of the rectosigmoid during a barium enema study in adults were observed in the Marion County General Hospital (Indianapolis), occurring within a year and a half of this incidence. A review of the medical records in this hospital revealed that these cases were the only perforations of the rectosigmoid that occurred in a 32 year period of record; during that time there were approximately 352,000 patients admitted. The records of the Indiana University Medical Center were also reviewed, and no adult cases of rectosigmoid perforation during a barium enema examination were found; these records did include I case of rectosigmoid perforation in a newborn infant, but the roentgenograms were not available.

The junction between the sigmoid and the rectum is difficult to localize precisely. The rectum begins where the sigmoid mesocolon ends, at the level of the third sacral vertebra. The term, rectosigmoid, is often used clinically, and it is used in this paper to designate the peritonealized portion of the colon between the last turn of the sigmoid and the anterior reflection of peritoneum off of the rectum.

The incidence of perforation of the normal rectosigmoid during a barium enema study is difficult to estimate. From conversations and a review of the literature, 10,12 it appears that many radiologists have had a case of perforation of the colon during a barium enema examination, with soiling of the peritoneal cavity as a result.

When these perforations occur in a normal colon, the rectosigmoid or a colostomy loop is usually the site. Passage of the barium enema suspension through a perforation caused by recent sigmoidoscopy appears to be one cause.¹ Puncture of the colon by an enema tip is another.¹¹ Hartman and Hills⁶ reported 2 cases of rupture of the colon in infants; they felt that these cases were due to overdistention of the rectosigmoid by the balloon of a rectal catheter.

Usually, the first clinical sign in perforation of the rectosigmoid is a sudden, sharp pain in the lower part of the abdomen; this pain is often followed by shock.¹ Fever, rapid pulse, and abdominal rigidity due to peritonitis develop within a few hours after the injury in many cases.^{2,11}

The diagnosis of perforation of the rectosigmoid is generally made immediately by the radiologist, at fluoroscopy; usually, the irregular streaks of barium between the loops of bowel are recognized. Roentgenograms will demonstrate this free barium and often free air in the peritoneal cavity.

Treatment of these perforations is medical management or prompt surgery with closure of the perforation and construction of a colostomy.¹²

The prognosis is always grave; the patient has about a 50 per cent chance of survival. Some reports indicate a better outlook if prompt surgery is done. 1,4

REPORT OF CASES

CASE I. This 63 year old man was admitted with the complaint of "gas on the stomach" for I week. This patient had been chronically ill for 3 years with complaints of epigastric pain and anorexia. One week before the present

admission, he developed constipation and vomiting. His past history was negative for prior surgery.

Marked ascites was present at the time of admission. Rectal examination revealed a circumferential rigidity that extended from the anus beyond the limit reached by the examining finger.

On the day of admission, a paracentesis was done and 1,000 cc. of straw-colored fluid was removed. Proctoscopic examination at this time revealed fungating, friable tissue, circumferentially involving the entire rectum, with secondary rigidity and stenosis. Biopsies were taken from 2 sites. The patient felt better the day following the paracentesis; his abdomen was nontender and his pulse was 76. During the next 4 days, he experienced no pain or nausea and the vital signs were normal. The biopsy specimens were verbally reported to the clinicians as showing no evidence of carcinoma. In an effort to diagnose the lesion, the patient was sent to the radiology department for a barium enema study, 5 days after the biopsy.

Because of the rigidity and stenosis, the Bardex balloon catheter could not be inflated in the rectum. Consequently, it was inserted more cephalad, into the rectosigmoid portion of the colon and then inflated. The barium enema flow was started. Fluoroscopy soon demonstrated barium in the left lateral gutter of the peritoneal cavity, coating the small bowel, and extending beneath the inferior edge of the liver. The Bardex balloon was deflated and the catheter was removed. Roentgenograms demonstrated the spill of barium (Fig. 1).

Following the perforation, the patient became acutely ill; his pulse rose to 160; respirations became 36 per minute, and fever spiked to 104°F. He also developed shock and cyanosis soon after this injury. He was treated with blood transfusion, intravenous fluids, and antibiotics. About 12 hours after the perforation he expired.

Autopsy the next day revealed a general peritonitis with approximately 2,000 cc. of thin, foul smelling fluid and barium in the peritoneal cavity. No fluid was present in the pleural or pericardial cavities. The liver weighed 470 gm., due to severe portal cirrhosis. Examination of the gastrointestinal tract revealed an adenocarcinoma of the gastric antrum with metastases to the pancreas, bladder, and rectum. There was no carcinoma in the rectosig-



Fig. 1. Case I. Roentgenogram demonstrating free barium in the left lateral gutter, of the peritoneal cavity, in the rectovesical pouch, over the upper lumbar spine, and to the right of the hepatic flexure.

moid, but there was a 7 cm. longitudinal perforation on its anterior surface.

CASE II. This 72 year old man was admitted with complaints of "prostate trouble" and constipation. The patient had difficulty voiding for 7 weeks and constipation for about 5 weeks before admission.

Physical examination at admission revealed an enlarged bladder, palpable just below the umbilicus. A tender, but nonincarcerated epigastric hernia was present. The rectal examination revealed a fixed prostate with multiple stone hard nodules along its upper margin; the rectal examination was otherwise normal.

About 1,100 cc. of clear urine was removed from the bladder on the day of admission. Cystoscopy revealed a tight prostatic urethra, a contracted bladder neck, and a trabeculated bladder with numerous cellules. The staff urologist recommended sigmoidoscopy to rule out carcinoma involving the rectum, and it was done to a distance of 15 cm. under atmospheric pressure. An extraluminal mass in the area of

the prostate was noted at a point 4 cm. cephalad to the anus; the mucosa was not involved. The rectum was negative except for this extrinsic mass.

Five days after sigmoidoscopy, a barium enema study was requested to rule out carcinoma of the colon. A Bardex balloon rectal catheter was inserted by the technician, and she rapidly pumped in 8 Baumanometer bulbs of air. The patient complained of sharp pain; there was a short delay before the barium enema flow was started. When the enema was administered, it immediately spread over the peritoneal cavity. The barium enema flow was stopped, and roentgenograms were made with the inflated Bardex balloon in place. The balloon was deflated after these roentgenograms had been taken, but it was not removed. The roentgenograms demonstrated the cephalad position of the inflated balloon and also barium streaks between the loops of bowel (Fig. 2).

One hour after the perforation, the patient's pulse was 96 and his systolic blood pressure was 95 mm. Hg by palpation. Surgery was begun 2 hours after perforation. When the peritoneal cavity was opened, air was released

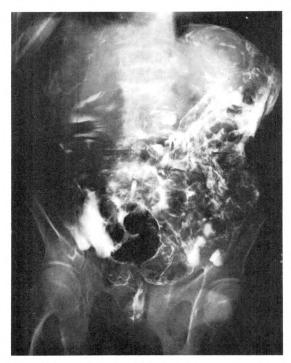


Fig. 2. Case II. The cephalad position of the inflated Bardex balloon and the multiple streaks of barium between the loops of bowel are apparent.

along with fluid feces that contained small flecks of barium. After the peritoneal incision was completed, a large amount of barium scattered throughout the peritoneal cavity was seen. The Bardex balloon was easily found; it protruded through a 7 cm. laceration of the rectosigmoid that began 4 cm. above the peritoneal reflection. The laceration ran parallel to the free taenial band; it was closed primarily. The peritoneal cavity was irrigated with large quantities of sterile saline with removal of considerable amounts of barium, and a divided loop colostomy of the transverse colon was formed. The patient was given 1,000 cc. of blood; he tolerated this 2 hour procedure well.

Postoperatively, the patient received an additional pint of blood and steadily improved. Fifteen days after the initial surgery, the colostomy was closed. A transrectal biopsy demonstrated carcinoma of the prostate about this time and an orchiectomy was done. About 2 months after admission, a transurethral resection of the prostate was performed. The patient tolerated each of these procedures well and was discharged ambulatory and cheerful.

CASE III. This 73 year old man was admitted with the diagnosis of chronic pulmonary tuberculosis, moderately advanced, activity undetermined. At the time of admission, the patient complained of weight loss, a cough productive of 2 cups of sputum daily, and hemoptysis. He did not have proven tuberculosis, but he had been on isoniazid and para-amino salicylic acid at home. His past history was noncontributory. After physical examination, the admitting impressions were: pulmonary emphysema, chronic pulmonary tuberculosis, arteriosclerotic heart disease with mild congestive heart failure, cataracts, and late latent syphilis with probable central nervous system involvement.

No acid fast bacilli were found on repeated sputum examinations. Chest roentgenograms during this admission demonstrated no change in the appearance of the scarred and emphysematous lungs. Upper gastrointestinal and barium enema examinations, performed 3 months after admission, were normal.

Eleven months after admission, but during the same hospitalization for pulmonary tuberculosis, the patient became progressively weaker, anorexic, and dehydrated. The cause of these changes was unknown. As part of an attempt to make a diagnosis, the patient was brought to the radiology department in a moribund state for a barium enema study.

A Bardex balloon rectal catheter was used. Barium had reached the splenic flexure when the fluoroscopist noted barium spreading out in streaks throughout the peritoneal cavity. The Bardex balloon catheter was deflated and removed. Roentgenograms confirmed the presence of a large amount of barium in the peritoneal cavity and free air under the diaphragm (Fig. 3).

Within 2 hours the patient underwent surgery. A large amount of barium sulfate was irrigated from the peritoneal cavity; a 3 cm. rent in the rectosigmoid, just above the peritoneal reflection, was found and closed. No disease was found in the remainder of the colon, small intestine, or stomach. The sigmoid colon was brought out as a loop colostomy.

Following surgery, the patient's condition continued to be grave; his blood pressure was 80/50, and his pulse was 88 approximately 12 hours after surgery. He expired the next day, and an autopsy was refused.

DISCUSSION

All of these cases had common factors:

- I. All patients sustained the laceration in the rectosigmoid.
- 2. A Bardex balloon rectal catheter (Virden model) was used in each case. These catheters were never heat sterilized and were flexible (Fig. 4).
- 3. Sigmoidoscopy was not done prior to the barium enema study. In the first 2 cases, it was performed 5 days previous to the study. In both of these cases, the patients were asymptomatic during this 5 day period so it is unlikely that sigmoidoscopic perforation could account for these rectosigmoid lacerations.

In 2 of the cases the Bardex balloon was definitely in an unusually cephalad position. In 1 case the balloon was intentionally

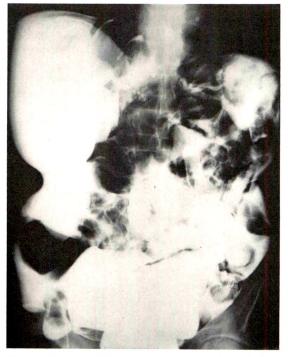
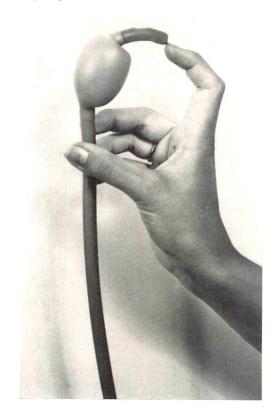


Fig. 3. Case III. The large amount of free barium in the peritoneal cavity and the free air between the barium coated right lobe of the liver and the diaphragm are seen.



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Fig. 4. The end of the Bardex balloon rectal catheter that has been "cold sterilized" is flexible.

placed above the contracted rectal ampulla, and, in the other case, its cephalad position was noted on roentgenograms and at surgery.

In the second case, the patient complained of pain during inflation of the Bardex balloon, not during the positioning of the uninflated balloon nor during the period when the barium was flowing into the colon. The time of pain in the other 2 cases is unknown.

These facts lead to the conclusion that at least 2 of these lacerations and probably the third were due to overdistention of the rectosigmoid by a Bardex balloon catheter that had been placed too far cephalad.

This mechanism of injury has been described and illustrated by Hartman and Hills (Fig. 5). They concluded that rupture of the normal colon at the time of barium enema examination is due to overdistention of the balloon of the rectal catheter at a point where the colon is narrowed and fixed by the peritoneal reflection. The balloon in the wide rectal ampulla could probably be fully inflated without injury.

The anatomic difference in the size of the rectal ampulla as compared to the rectosigmoid is striking when one examines a routine barium enema study. Gorsch⁵

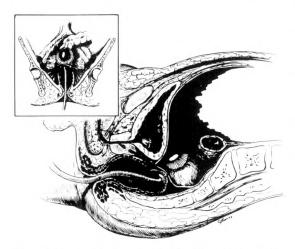


Fig. 5. The mechanism of perforation of the rectasigmoid by a balloon catheter that has been placed too far cephalad. (Reproduced by permission of Drs. Hartman and Hills, *Annals of Surgery*, and I. B. Lippincott Company.)

states that the circumference of the rectosigmoid is approximately 15 cm., whereas the rectal ampulla has a circumference of 35 cm. or more.

The tolerance of large caliber intestinal segments, such as the rectal ampulla, has been shown to be less than the tolerance of small caliber segments for the same transmural pressure because of the Law of LaPlace, i.e., the tension tending to tear apart the wall of a cylinder is the product of the change in pressure across the wall times the radius of the cylinder. However, the pressure exerted by an inflated balloon against the wall of a tight-fitting segment of sigmoid is greater than the pressure exerted by a balloon of the same volume against the wall of an ampulla that probably does not even make circumferential contact with the balloon. Also, since the rectal ampulla is surrounded by pelvic soft tissue (Fig. 5), the change in pressure across its wall, i.e., the transmural pressure, will be little, for much of the balloon pressure will be transmitted to the pelvic soft tissue. The rectosigmoid is, of course, free of supporting soft tissue and would bear a large change in pressure across its wall when distended by a balloon. The same situation is present when a balloon is inflated in a colostomy loop.

Thus, because of its large diameter and support by surrounding pelvic soft tissue, the rectal ampulla is an ideal receptacle for the distended balloon of a rectal catheter. When the balloon is in the rectal ampulla, distention of the balloon by a large volume of air is possible. Nathan and Kohen⁸ report using 400 cc. of air to inflate the balloon in 1 patient; this volume of air is equal to approximately 13 Baumanometer bulbs of air.

Since it may be difficult to locate the balloon in relation to the rectal ampulla at fluoroscopy, positioning of the balloon in the ampulla can be assured by pulling down on the balloon to seat it against the anal sphincter, after pumping in 1 or 2 bulbs of air.

Because the 3 cases of rectosigmoid per-

foration presented here appear to have been due to balloons placed too far cephalad and since these 3 cases were the only rectosigmoid perforations found in the records of one hospital, it appears likely that this mechanism of perforation accounts for a relatively large number of the traumatic perforations of the rectosigmoid. This same mechanism is probably also responsible for perforation of colostomy loops by inflated balloons.

SUMMARY

Three cases of perforation of the rectosigmoid are presented. A flexible Bardex balloon rectal catheter was used in each of these 3 patients and there was no instrumentation of the colon just prior to perforation. In 2 of the cases, the balloon was definitely in the rectosigmoid when inflated. A technique to prevent some of these perforations is suggested.

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I am grateful to Dr. William A. Tosick, Director of the Department of Radiology of the Marion County General Hospital (Indianapolis), for pointing to the mechanism of perforation in these cases and to Dr. Arvine G. Popplewell, Superintendent of the Marion County General Hospital, for permission to publish these cases.

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EOSINOPHILIC (ALLERGIC) GASTROENTERITIS*

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EOSINOPHILIC gastroenteritis has not been given sufficient consideration in the roentgenologic diagnosis of small bowel disorders. The description of this entity did not appear in the radiologic literature until 1964,³ probably because the roentgenologic appearance in the small bowel is similar to that of regional enteritis.

The eosinophilic form of gastroenteritis is characterized by a wall, thickened in one or several regions of the alimentary tract by a diffuse infiltrate of predominantly mature eosinophils. The review of the literature by Ureles et al.17 in 1961 revealed 25 cases of this disease entity. Edelman and March,3 in 1964, accepted the diagnosis of eosinophilic gastroenteritis as correct in 24 instances of their own and of previously reported material. The largest individual report is that of McCune, Gusack, and Newman, in 1955, with 3 cases. We believe that eosinophilic gastroenteritis is more common than initially believed. Now that instruments for biopsy of the small bowel are available, the diagnosis of eosinophilic gastroenteritis should be made more readily and frequently.

We have seen the typical clinical and roentgenologic manifestations of eosino-philic gastroenteritis in 7 patients. The diagnosis was proved histologically in 4 and these patients are the subject of this report.

For diagnostic data relating to diseases of the bowel, the clinician depends on the roentgenologist. The roentgenologist, therefore, should be aware of the clinical and roentgenologic criteria necessary to establish the diagnosis of eosinophilic gastroenteritis.

This presentation is not concerned with the so-called "eosinophilic granuloma" of the gastrointestinal tract, a circumscribed polypoid lesion with the roentgenologic appearance of an extramucosal, intramural filling defect. It has been described in the stomach,¹² and in the small¹⁶ and large bowel,¹¹ but has not been related to the eosinophilic granuloma of bone or lung. Blood eosinophilia, as that in eosinophilic gastroenteritis, is not seen in eosinophilic granuloma of the gastrointestinal tract.

REPORTS OF CASES

CASE I. A 31 year old woman was admitted to the University of California Hospital, San Francisco, because of abdominal symptoms of 6 weeks' duration. Associated with these were bouts of diarrhea and constipation, intermittent cramping, diffuse supra-umbilical pain, vomiting, and aggravation by laxatives. She gave a history of allergic rhinitis, particularly from weeds and grasses.

On physical examination the abdomen was moderately distended and a shifting dullness was noted. Abdominal paracentesis revealed ascites containing eosinophils. Significant laboratory data were 11,000 white blood cells per cu. mm. with 36 per cent eosinophils. The results of stool examinations were negative for ova and parasites.

The roentgenologic appearance of the small bowel on admission was interpreted as regional enteritis (Fig. 1).

Exploration of the abdomen yielded 1,500 cc. of ascitic fluids. Small bowel biopsy revealed the submucosa to be edematous with an infiltrate of eosinophilic cells through all layers. The histologic diagnosis was eosinophilic enteritis (Fig. 2).

One year later the patient was re-admitted for evaluation of dysuria which had been present for 4 weeks. An excretory urogram showed marked thickening, up to about 3 cm., of the entire bladder wall (Fig. 3). A biopsy revealed eosinophilic cystitis. On microscopic examination dense infiltration of the stroma with eosinophils was noted. The presence of eosinophilic cystitis in this patient was reported previously. The white blood cell count was 27,000 per cu.

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Fig. 1. Case 1. Small bowel study on admission showed irregular narrowing of loops of small bowel with thickening and rigidity of wall.

mm. with 80 per cent eosinophils. The examination of the urine showed 3 to 5 white blood cells per high power field with occasional eosinophils. The results of stool examinations were again negative for ova and parasites.

Cortisone therapy was administered and reexamination of the small bowel 3 months later showed that the intestinal pattern had returned to normal (Fig. 4).

On re-examination 5 years after the first admission, the pattern of the small bowel con-

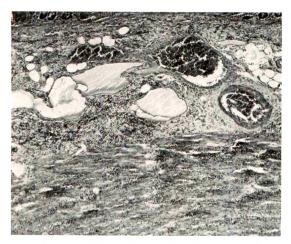


Fig. 2. Case I. Photomicrograph of biopsy specimen of small bowel. A dense infiltrate of eosinophils is seen throughout all layers.

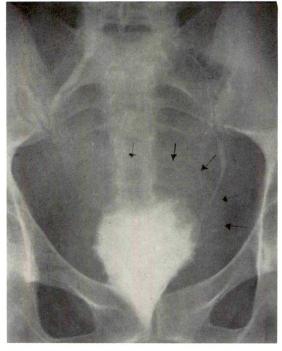


Fig. 3. Case i. Excretory urogram showed up to 3 cm. of thickening of the entire bladder wall.

tinued to be normal (Fig. 5). No intestinal or urinary complaints were elicited. At present, $6\frac{1}{2}$ years after the original admission, the pa-



Fig. 4. Case I. Re-examination of the small bowel 3 months after continued prednisone therapy showed intestinal pattern returned to normal.

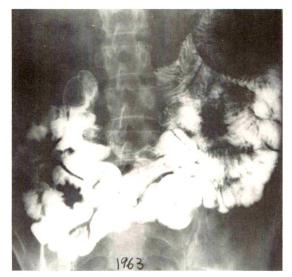


Fig. 5. Case I. Small bowel re-examined after 5 years of prednisone therapy showed a normal roentgenologic pattern.

tient continues to take 5 mg. of prednisone daily and is free of symptoms.

Case II. This 55 year old woman was referred to the University of California Hospital, San Francisco, with a history of left lower quadrant abdominal pain of 6 months' duration. For the last 2 weeks the pain had been accompanied by diarrhea. The patient had had asthma for many years and gave a history of an allergy to feathers and house dust.

The results of the physical examination were entirely within normal limits. Laboratory data showed 8,550 white blood cells per cu. mm. with 10 per cent eosinophils. The results of stool examinations on 3 occasions were positive for guaiac reaction, but negative for ova and parasites. On gastric analysis, free acid was present only after stimulation with histalog.

Roentgenologic study of the upper gastrointestinal tract gave evidence of an irregularity in the antrum, consistent with carcinoma. Pronounced pylorospasm was noted (Fig. 6). A diagnosis of carcinoma was made. Pliability and peristalsis were present, however, by cinefluorography and polygraphy (Fig. 7). The small bowel study showed no abnormality.

Gastroscopy confirmed an infiltrative process in the distal stomach. At surgery, the gastric wall was thickened to more than I cm. The distal stomach appeared to be infiltrated. The biopsy revealed a cellular infiltration in the



Fig. 6. Case II. Upper gastrointestinal study showed an irregular infiltrate along the distal half of the greater curvature and of the antral portion of the lesser curvature. Pronounced pylorospasm.

submucosa and muscularis consisting predominantly of eosinophils. The infiltrate was distributed in a perivascular pattern. The histologic diagnosis was eosinophilic gastritis.

The patient was discharged with instructions



Fig. 7. Case II. Three exposures on I roentgenogram (polygraph). Peristalsis along the area of infiltration.

to continue cortisone. Roentgenograms repeated I year later showed the gastrointestinal tract to be completely normal (Fig. 8).

For the past 4 years the patient has been free of intestinal symptoms during which time cortisone therapy has been continued.

Case III. A 57 year old man was admitted to the University of California Hospital, San Francisco, with a history of allergy since childhood, resulting in severe urticarial reaction and chronic bronchitis. A strong family history of allergy was obtained. Three months before admission severe paroxysms of asthma, recurrent abdominal bloating, cramping, meteorism, and diarrhea developed.

On examination the abdomen was moderately distended. The laboratory studies of the blood revealed 5 eosinophils per high power field. Stool examinations gave negative results for ova and parasites. Roentgenologic studies of the small bowel showed slow transit, dilatation of several loops and thickening of the intestinal wall (Fig. 9). A biopsy of the small bowel showed a cellular infiltration of the mucosa consisting predominantly of mature eosinophils, diagnosed histologically as eosinophilic enteritis. Prednisone was prescribed, and the patient was discharged. At present, I year after admission, he is without symptoms.



Fig. 8. Case II. Follow-up study I year after Figure 7.

Normal roentgenologic appearance of the greater curvature. The site of gastrotomy is seen on the lesser curvature.



Fig. 9. Case III. Small bowel study showed distention of several loops and thickening of the intestinal wall.

Case IV. A 52 year old woman was admitted to the University of California Hospital, San Francisco, with a chief complaint of abdominal pain of 3 months' duration. Duodenal ulcer was suspected and the patient was treated by the Sippy regimen and antacids. The pain continued, however. Upper gastrointestinal roentgenograms revealed an incomplete filling of the antrum and duodenal bulb, suggestive of duodenal ulcer (Fig. 10). On 3 of 5 blood cell counts, the number of eosinophils was normal. The leukocyte count was elevated to 9 and 20 per cent on two other occasions. The results of stool examinations were negative for ova and parasites. At operation, the pyloric region was thickened and a partial gastrectomy was performed. The histologic examination showed edema of the submucosa and muscularis and a cellular infiltration composed primarily of eosinophils. The infiltrates were particularly clustered around the small vessels. A histologic diagnosis of eosinophilic gastroduodenitis was made (Fig. 11).

DISCUSSION

Although the allergic manifestations of the skin are well understood, little is known about tissue hypersensitivity of the internal surfaces of the human body. The cause of eosinophilic gastroenteritis is unknown, but the strong family history of allergy in most patients with this entity may be of significance. In favor of a hypersensitivity or an

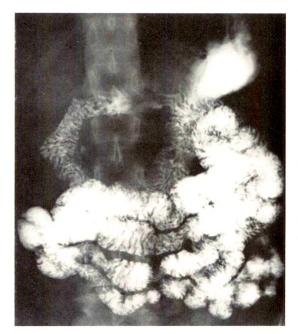


Fig. 10. Case IV. Upper gastrointestinal study revealed incomplete filling of the antrum. Duodenal ulcer disease was suggested, but no crater was seen. Gastric emptying was delayed. Duodenal diverticulum noted incidentally.

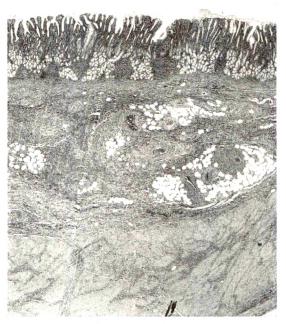


Fig. 11. Case IV. Photomicrograph of biopsy specimen of the thickened gastric wall showed eosinophilic infiltration involving all layers from mucosa (top) to serosa (lower right).

allergic reaction in eosinophilic gastroenteritis is the involvement of multiple organs (Case 1). Eosinophilic gastroenteritis associated with eosinophilic peritonitis, eosinophilic cystitis, bronchitis, asthma has not been reported previously. The prominent eosinophilia, which has been reported as high as 63 per cent in eosinophilic gastroenteritis, also suggests an allergic cause. In one of our patients (Case 1), eosinophilia of 80 per cent was noted. These eosinophils are always mature cells. Perivascular distribution of the cellular infiltrates further favors an underlying allergic reaction in eosinophilic gastroenteritis.5

The concentration of eosinophils observed histologically in eosinophilic gastroenteritis is more pronounced than in other pathologic states. Ureles *et al.*¹⁷ have emphasized that eosinophils are a normal component of gastrointestinal tissue⁷ and are seen in increased concentration in Hodgkin's disease,² gastrointestinal carcinoma,¹⁸ amebiasis,¹ helminthic disease,⁹ and gastric ulcers.

When associating eosinophils with hypersensitivity reactions, the limited knowledge about the function of the eosinophilic cell must be taken into consideration. Robbins¹³ stated, "While these cells are believed to have the same chemotactic and phagocytic potentialities as the neutrophil, they do not contribute to the defensive response in any fashion comparable to the contribution of the neutrophilic leucocytes. They appear to be under the control of the adrenal cortical hormones, excess of which brings about their disappearance from the blood." Speirs¹⁴ found that eosinophilia in the blood stream results at once from injection of a protein antigen, but only in the sensitized animal. He expressed the belief that eosinophils are possibly involved in the production of antibodies.15

That an allergic reaction of the gastrointestinal surfaces represents the underlying etiology in eosinophilic gastroenteritis might reasonably be assumed when: (a) eosinophils are especially attracted by the antigen-antibody reaction; (b) the eosinophil count is typically high in patients with proved eosinophilic gastroenteritis; and (c) a strong history of allergy is obtained.

The roentgenologic appearance in eosinophilic gastroenteritis is fairly typical and should suggest the diagnosis to the roentgenologist familiar with this entity. Morphologic changes in the stomach are usually limited to the distal half or to the antrum. The infiltrative process results in an irregular gastric outline. The roentgenographic appearance is that of a mass resembling carcinoma. If pliability and peristalsis are present, differentiation from carcinoma may be possible, especially with the use of cinefluorography. Tumor-like infiltrations in the gastric antrum disappearing within a few days have been reported.6 Gastric involvement may be reflected only by delayed gastric emptying and pylorospasm. Involvement of the stomach was present in all 25 of the patients reviewed by Ureles and associates.¹⁷ The only reports of no gastric abnormality on roentgenologic examination are those of our 2 patients (Cases 1 and 111).

In one patient described by Edelman and March,³ the additional feature of a protein-losing enteropathy was present with gastric involvement. Our patients were not studied for this phenomenon.

The small bowel, in addition to the stomach, was involved in about half the patients reported by Ureles *et al.*¹⁷ The first reports of involvement of small bowel alone are those of our 2 patients (Cases 1 and 111). The roentgenologic changes of eosinophilic gastroenteritis involving the intestine are similar to those of inflammation or granulomatous disease, as seen in regional enteritis. Segments of the small bowel show thickening of the wall, rigidity, and narrowing of the lumen.

Eosinophilic gastroenteritis is more readily diagnosed roentgenologically if combined gastric, pyloric, and small bowel involvement is present, particularly in the presence of blood eosinophilia. Edelman and March³ pointed out that the combina-

tion of antral narrowing and eosinophilia should alert the roentgenologist to the possibility of eosinophilic gastroenteritis.

The roentgenologic differentiation between eosinophilic gastroenteritis affecting the small bowel only and regional enteritis may be impossible. With eosinophilic gastroenteritis, additional gastric involvement is usually present, whereas regional enteritis rarely occurs in both areas of the alimentary tract. If the roentgenologic appearance indicates that eosinophilic gastroenteritis is limited to the antrum, then other diseases must be considered. These are gastric carcinoma, antral gastritis accompanying peptic ulcer, tuberculosis, syphilis, and isolated granulomatous gastritis.4

A characteristic clinical feature to remember is the self-limitation of eosinophilic gastroenteritis and its response to cortisone therapy. If the small bowel appears normal after a previous roentgenologic diagnosis of regional enteritis, the diagnosis of eosinophilic gastroenteritis may have been correct. We have seen 3 additional patients with blood eosinophilia and the described roentgenologic changes of either stomach or small bowel. In 2, a biopsy could not be obtained and cortisone therapy was tried before deciding upon exploration. Both patients responded well and the roentgenologic appearance returned to normal after this therapy. In the third patient, the antrum, pylorus, and small bowel were involved. After duodenal intubation and biopsy, negative results were obtained on histologic examination. Another biopsy at a more distal intestinal level was refused and the patient was treated with cortisone. On re-examination, the roentgenologic appearance of all 3 areas of the intestinal tract had returned to normal as had the number of eosinophils.

SUMMARY

Four cases of eosinophilic (allergic) gastroenteritis are reported, including the first reports of involvement limited to the small bowel.

The roentgenologist's role in the diagnosis of eosinophilic gastroenteritis is important. This condition should be considered in patients with peripheral eosinophilia and with the described roentgenologic changes in the stomach and small bowel. An allergic reaction of the gastrointestinal surfaces is considered a likely explanation for eosinophilic gastroenteritis.

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We are grateful to Drs. Phillip L. Pillsbury and Glen Bell for permission to include their case.

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EROSION OF RETAINED SURGICAL SPONGES INTO THE INTESTINE

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INTRAPERITONEAL foreign bodies of any origin, such as gallstones, appendicoliths, bullets, and a host of surgical accessories may remain inert, result in a low grade chronic smoldering peritonitis or in a fulminating infection. A most unusual occurrence is the erosion of a foreign body into the intestinal lumen (presumably in an attempt to rid the body of an irritant).

The following 3 cases are presented to illustrate the roentgenographic patterns of this phenomenon.

REPORT OF CASES

Case I. A 66 year old male was admitted to the hospital with complaints of abdominal pain, anorexia, weight loss and constipation. During the preceding to days, he had a low grade fever and a severe productive cough. Six months prior to admission, the sigmoid colon had been resected for diverticulitis and the postoperative course was marked by a wound infection, dehiscence and the formation of a fecal fistula. Following repair of the wound and control of the infection with antibiotics, he was discharged to be followed at home.

On physical examination, a large ventral hernia and generalized abdominal distention and tenderness were noted. No masses were palpated but there was shifting dullness and other signs of ascites. On abdominal roentgenograms, fine detail and soft tissue outlines were obscured by the ascitic fluid but the radiopaque tape of a laparotomy pad was present in the right lower quadrant (Fig. 1). Lateral views localized the tape midway between the vertebrae and the anterior abdominal wall. A finely honeycombed and indistinctly outlined soft tissue mass, approximately 10 cm. in diameter, was visible just above the tape. On small bowel examination, barium coated and infiltrated the large mass demonstrating its intraluminal location, and a small amount of barium passed through a fistula into the hepatic flexure (Fig. 2 and 3). Loops of bowel adjacent

to the mass were adherent to each other and distorted.

On surgical exploration, a laparotomy pad was found surrounded by fibrin, and exudate covered loops of tightly adherent ileum. Pseudopodial extensions of the edges of the pad had eroded through the wall of the ileum into its lumen in 4 different areas, and in 1 of these areas the ileum was distended by a large rolled-up portion of the pad. There was, in addition, a fistula between the dilated loop of ileum and the adjacent transverse colon.

Following resection of 4 feet of ileum the patient made a rapid and complete recovery.

Case II. A 45 year old female was admitted to the hospital because of severe crampy abdominal pain and vomiting for a period of 10 days. Similar complaints but much milder in severity had been present since gynecologic

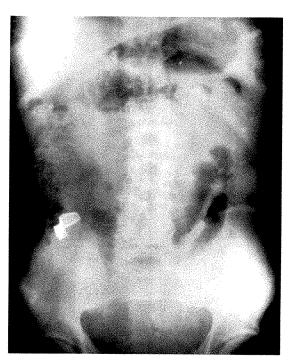


Fig. 1. Case 1. The finely honeycombed pattern of the gas and secretion impregnated laparotomy pad is visible just above its radiopaque tape.

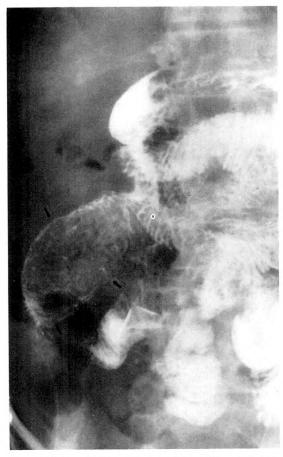


Fig. 2. Case I. Barium coats a large filling defect in the ileum on the 30 minute small bowel roentgenogram.





Fig. 4. Case II. The finely mottled soft tissue mass displaces the ascending colon medially. Note the egg shells to the left of L5.

surgery 2 years prior to admission. Abdominal examination showed a soft tender easily movable mass in the right upper quadrant and high pitched bowel sounds were present in the same area.

On abdominal roentgenograms a frothy, sponge-like, 4 cm. wide sausage-shaped mass of soft tissue density was demonstrated lateral to the ascending colon extending from the hepatic flexure to the iliac crest (Fig. 4). There was, in addition, a 7 cm. collection of faint short curvilinear calcific densities, centered over the inferior articular process of L₅. A few loops of distended small bowel occupied most of the epigastrium and left upper quadrant. On small bowel examination, barium coated and perme-

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Fig. 3. Case I. At 4 hours, barium coats and fills the interstices of the laparotomy pad. At surgery, there was a fistula to the hepatic flexure in the region marked by the two arrows.

ated the interstices of the right flank mass (Fig. 5), demonstrating it to be intraluminally located in the distal ileum. The barium also obliterated the curved calcific densities.

At laparotomy, the palpable mass was shown to consist of a distended necrotic loop of ileum containing a rolled-up laparotomy pad. Several loops of small bowel were adherent to each other, to the necrotic loop and the anterior abdominal wall. The small bowel proximal to the mass was obstructed and dilated and contained fragments of egg shell.

Following resection of the involved bowel, the patient made a rapid recovery. The reason for the absence of a radiopaque marker on the pad could not be determined. Upon subsequent questioning, the patient admitted swallowing egg shells.

Case III. In this case, the only history available pertained to the surgical findings. There was a chronic type of fibrinous and fibrous peritonitis with loops of bowel tightly adherent to each other. The involved loops of bowel were



Fig. 5. Case II. Note barium permeating the interstices of the sponge.



Fig. 6. Case III. The radiopaque thread is seen adjacent to the cecal area.

resected and a sponge was found entirely within the lumen of the ileum.

The initial roentgenogram showed many dilated loops of small bowel and a radiopaque thread of a 4×4 inch pad in the area of the cecum (Fig. 6). On small bowel examination, the pad was clearly defined as a radiolucent mass within a segment of dilated ileum and the opaque thread was still seen (Fig. 7).

DISCUSSION

Of the varied consequences of intraperitoneal retention of a surgical sponge, the most unusual is the erosion of the sponge into the intestine. Crossen and Crossen,³ in an extensive survey, found 37 cases in which the retained sponge was eventually passed per rectum. They also found 24 cases in which the sponge was entirely within the lumen of the bowel and in 10 cases the sponge was partially intraluminal. They noted that elimination of the sponge may occur as soon as 2 weeks following laparotomy or be delayed as long as 5 years.



Fig. 7. Case III. The pad within the ileum is outlined by arrows. Note the thread within the bowel at the upper arrow.

The mechanism by which a sponge erodes through the bowel wall was demonstrated in Case I. The sponge is encapsulated by loops of ileum and the inflammatory products of peritoneal reaction. In one or more areas, necrosis of the wall occurs and a fold of the sponge penetrates into the lumen of the bowel. Under favorable circumstances, peristalsis propels the lead mass forward dragging the remainder of the sponge through the bowel until it is eliminated. However, where there are multiple perforations, as in Case 1, or where there are small bowel kinks or strictures, the sponge becomes impacted and obstruction results.

On roentgenograms, sponges and pads while still entirely within the peritoneum are identified by opaque markers, occasionally, in association with a homogeneous soft tissue mass. Following perforation of the bowel wall, the gauze becomes infil-

trated with secretions and gas and a honeycombed pattern is then seen on the roentgenogram. This appearance resembles feces but the constancy of location and pattern eliminates this possibility from consideration.

On roentgen studies of the small bowel, there is a considerable degree of distortion. Loops of intestine are adherent to each other and to the adjacent structures. The intestinal wall is thickened and there is a grossly irregular mucosal pattern which may be coarsely serrated, scalloped or edematous. There is, however, no fixation or rigidity of pattern except in association with ulceration. Segments of narrowing and dilatation are usually found. Where there has been perforation of the bowel wall without penetration of the pad into the lumen, barium may permeate into the folds and the mesh of the gauze. When there has been intrusion of the sponge into the lumen, the bowel wall is expanded around the barium coated foreign body. The over-all pattern closely resembles that of lymphosarcoma of the small bowel.5

SUMMARY

Retained surgical sponges are identifiable by radiopaque markers, and, when lost, can be expeditiously located by roentgen examination. However, by a rare chain of circumstances, sponges may be left in the peritoneum unwittingly only to make their presence known weeks or years later. These gauze pads are easily recognized on roentgenograms before perforation occurs by a radiopaque marker and a mass of soft tissue density. Following perforation of the bowel wall, barium floods the interstices of the sponge and when the sponge becomes intraluminal in location, the bowel wall becomes distended by the barium impregnated mass.

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THE ROENTGEN ASPECTS OF SOME APPENDICEAL ABNORMALITIES*

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THE vermiform appendix represents a small segment of the gastrointestinal tract. However, diseases related to this vestigial organ are of great importance in daily medical practice. Present day knowledge of inflammatory diseases of the appendix was initiated by Fitz in a publication in 1886.¹⁰ Since then the subject of appendiceal disease, particularly acute inflammatory appendicitis, has assumed increasing importance. Yet other appendiceal abnormalities are being recognized with increasing frequency.

The diagnosis of acute appendicitis is most often made by history and the physical signs in the acute state. Malpositions and neoplasms when present are usually encountered surgically at the time of laparotomy. Systemic, diffuse, or generalized intestinal disorders which also involve the appendix, are diagnosed either preoperatively with the use of contrast medium by the radiologist or by the surgeon at the time of laparotomy. The use of plain roentgenograms in the diagnosis of appendiceal disease is not always appreciated. It is the purpose of the authors to summarize briefly the role of the roentgen modality in the diagnosis of appendiceal disorders with emphasis on the use of plain roentgenograms.

It is obvious that the rewards of the effort will depend not only on the sophistication of the clinician in requesting the roentgen examination for suspected appendiceal disease, but also upon the astuteness of the roentgenologic interpretations. It is also apparent that the roentgen changes in appendiceal disease reflect a

combination of factors including the various anatomic positions of the appendix, the extent of changes in the appendix and the effect on neighboring bowel and soft tissue structures. Thus the diagnosis will depend on the accurate demonstration of distortive changes in the appendix itself or on the inferential data obtained roent-genographically by observed alterations in associated structures.

VARIANTS

The anlage of the appendix first appears between $6\frac{1}{2}$ to 8 weeks of uterine life, becoming clearly defined at 10 to 12 weeks when the cecum is subhepatic, and the ascending colon is not yet delineated. The position of the appendix is varied and is determined by the following factors: the degree of descent of the cecum; the degree of cecal fixation to the posterior abdominal parietes; the configuration of the cecum; the length of the appendix (normally in the range of I to 91 inches); the degree of development of the pericecal fossae; the presence of associated adhesions (whether they arise from the appendix or associated organs); the presence and extent of submucosal lymphoid hyperplasia; and the habitus of the individual.

There are numerous normal variations in the position of the appendix so that it may assume actually any of the positions of the hand of a clock with the center considered as the site of appendiceal origin.

According to Treves,²⁹ there are four basic anatomic variations of origin of the appendix from the cecum. These may be tabulated as follows:

1, 1905.
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Type I. The fetal type. In this type the appendix arises from the apex of the cecum and forms a continuation of the long axis of the colon (Fig. 1).

Type II. The cecum is roughly quadrilateral in shape and the appendix appears between two bulging cecal sacculi instead of at the summit of the colon, as in the fetal type (Fig. 2).

Type III. In this, the most common type, the portion of the cecum lateral to the origin of the appendix bulges and the base of the appendix arises from the medial wall. The apex of the cecum is positioned medially. Therefore, a false apex is formed by the highly developed portion lateral to the appendiceal origin (Fig. 3).

Type IV. Here the appendiceal origin is close to the ileocecal valve without any trace of the original apex of the cecum (Fig. 4).

The patterns of complications of appendiceal disease, with reference specifically to abscess formation and intestinal obstruction, are a direct function of the anatomic position of the appendix. In two reviews summarizing a total of 75,000 appendectomies, it is stated that the appendix is usually an intraperitoneal organ lying anterior to the cecum or in line with it. However, there is general agreement that about



Fig. 1. The fetal type cecum which is characterized by a gradual continuation of the cecum into the appendix in a conical or triangular fashion. The appendix appears as a tubular extension of the conical cecum as seen on this spot roentgenogram.



Fig. 2. The appendix arises between two prominent cecal sacculi of the apex of the cecum in this spot roentgenogram.

25 per cent of appendices lie in a retrocecal position. The retrocecal appendix may be either intraperitoneal, extraperitoneal, or

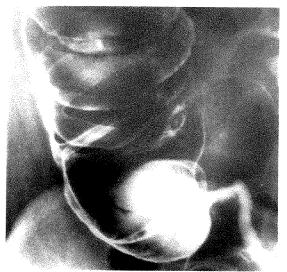


Fig. 3. The appendix arises from the medial wall of the cecum below the ileocecal valve with a prominent bulging lateral cecal pouch which is a false cecal apex. The ileocecal valve is well visualized in this barium-air contrast study of the cecum.



Fig. 4. The appendix arises close to the ileocecal valve in this spot roentgenogram.

may be free in the retroperitoneal position. Of the retroperitoneal appendices, 60 per cent are in a fixed retrocecal position and 40 per cent are in a mobile retroperitoneal position. 4.5,27

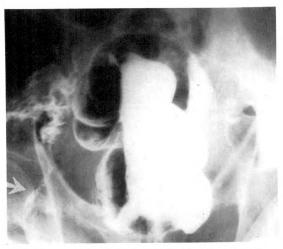


Fig. 5. A barium filled appendix is visualized in a right femoral hernia on this barium-air contrast study of the colon.

The roentgen changes in the retroperitoneal or retrocecal appendix are less marked than in those appendices which are positioned anterior to or in line with the cecum. This retroperitoneal position of the cecum is definitely a limiting factor in the diagnosis of appendiceal disorders on the plain roentgenogram.

Of the group of appendices (75 per cent) which lie in a position anterior to the cecum, there are 3 major categories: those which lie caudad (about 29 per cent of the total); those mesial to the cecum (approximately 38 per cent); and that group lateral to the cecum (6 per cent of the total).^{4,5}

ABNORMALITIES OF APPENDICEAL POSITION RELATED TO ABNORMALITIES IN POSITION OF THE CECUM

The appendix, as an elongated variably mobile tube, may present in numerous ectopic positions within the peritoneal cavity as well as in extraperitoneal spaces. Such mobility is possible in instances where the cecum and ascending colon have a well developed mesentery or are loosely fixed to the posterior abdominal parietes.

Collins^{5,6} has described the appendix in external hernias in 1.1 per cent of autopsy and surgical specimens. These illustrated cases of hernia, containing appendices, are directly related to the capability of a non-adherent appendix, arising from a loosely supported cecum, to assume a position in a pre-existing hernia. Such ectopic positions of the appendix are demonstrated in Figures 5; 6, A and B; 7; 8; and 9.

Clinicians are well aware that there is frequently a differential diagnostic problem relating to acute appendiceal disease and diseases occuring in the gallbladder, the right kidney, and the base of the right lung or pleura. Such a differential diagnosis has its basis in the various anatomic positions of the appendix.

APPENDICEAL CONCRETIONS

The association of appendicoliths with acute appendicitis has been the subject of numerous recent publications.^{2,16,23,24} The

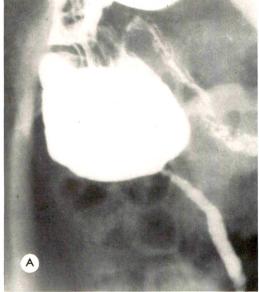




Fig. 6. (A and B) Barium enema studies demonstrate



Fig. 7. The appendix and cecum are seen in a left ventral hernia in this anteroposterior barium enema roentgenogram.

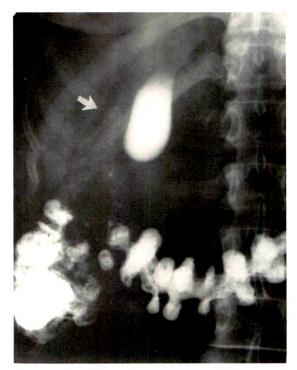


Fig. 8. A gas filled subhepatic appendix is outlined adjacent to a contrast filled gallbladder in this anteroposterior projection of the abdomen.

the cecum, appendix, and loops of ileum in a sliding right inguinal hernia.



Fig. 9. A barium filled appendix is seen in a right foramen of Morgagni hernia. There is associated failure of rotation and descent of the cecum and ascending colon as shown in this barium enema study. (Courtesy of Dr. Murray Rosenzweig.)

clinical-pathologic correlation, however, was well established by Kelly¹⁵ in his comprehensive monograph published in 1905, in which he presented numerous illustrations of this entity and commented clearly on the significance of the association of coproliths and appendicitis. According to Felson and Bernhard,8 the first roentgen diagnosis was made by Weisflog³¹ in 1906. It remained for Wangensteen and Dennis³⁰ to emphasize the role of obstruction as a factor in the pathogenesis of acute appendicitis. The published reports uniformly emphasized the severity of the inflammatory process in patients with a roentgen demonstration of appendiceal calculi.

An appendicolith is to be distinguished from a nonopaque fecolith. The latter

represents a ball of fecal material which is not significant in the same way as the calcium-containing intraluminal appendiceal stone. The fecolith represents a localized inspissated form of fecal matter and mucus in which there are incorporated numerous bacteria. Fecoliths are not discernible on the plain roentgenogram of the abdomen. However, most localized collections of fecal material are demonstrable on barium enema study where the appendiceal lumen can be filled. Such fecoliths present as multiple, round, well-circumscribed filling defects in the appendix as illustrated in Figure 10. The term coprolith or appendicolith should be reserved for true stones which contain inorganic matter as well as calcium phosphate and fecal material. Such coproliths are usually demonstrable on a plain roentgenogram of the abdomen, depending on size and degree of calcification. The nucleus of the calculus is often inspissated fecal material although it may occasionally be represented by a foreign body or even by a true gallstone which has found its way into the appendiceal lumen. These appendicoliths are frequently laminated and often conform to the configuration of the appendiceal lumen. They are

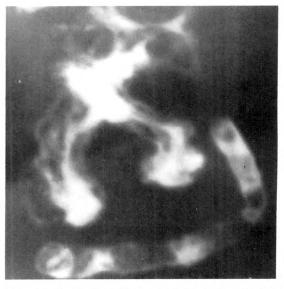


Fig. 10. A barium filled appendix with multiple rounded radiolucencies characteristic of fecoliths.

roentgenographically demonstrable about 10 per cent of adult patients with acute appendicitis, and are multiple in about one-third of the cases encountered.8 These stones are believed to arise in the appendix as a concretion containing calcium, vegetable fibers, mucus and bacteria. Roentgenographically, some of these concentric laminated calculi resemble gallstones and are differentiated from them only with great difficulty. Most appendicoliths arise primarily in the appendix although little else is known regarding their true etiology. They differ in composition from both enteroliths and biliary calculi. Faegenburg's study of 100 cases of acute appendicitis confirms the fact that calculi were visible in about 12 per cent of these patients, while in 100 patients with noninflamed appendices a coprolith was seen in only I patient. The presence of coproliths, in association with symptoms, is almost diagnostic of inflammatory appendiceal disease. In a rare instance in which the appendix is not inflamed clinically, in the presence of a coprolith such an appendix is especially susceptible to obstructive and perforative changes. Generally, patients with the signs of acute appendicitis and roentgen evidence of coproliths present with advanced stages of appendiceal disease. Felson and Bernhard⁸ and Shaw²³ point out that in approximately 50 per cent of such patients the appendix is actually perforated. The differential diagnosis of such a right lower quadrant concretion must include right ureteral calculus, enostosis of the ischium or ilium, calcified mesenteric lymph node, gallstone, phlebolith, or an ingested pill. The roentgen demonstration of patients with appendicitis presenting with coproliths of the appendix is illustrated in Figures 11 through 17.

INFLAMMATORY DISORDERS OF THE APPENDIX WITHOUT COPROLITHS

A fuller awareness of the role of the roentgen modality in the diagnosis of inflammatory disorders of the appendix will produce a significantly high yield. We have



Fig. 11. An oblique roentgenogram of the abdomen demonstrates an appendicolith and reflex ileus in a child with acute appendicitis.

found it a wise and productive policy to examine all patients roentgenographically for suspected appendiceal disease. Frimann-Dahl11 states that positive roentgen findings have appeared in about 50 per cent of 150 cases examined in his department in Norway. The possibility of observing roentgen changes is a function of the position of the appendix as well as of the extent of the inflammatory process; of prime importance here is whether or not the inflammatory process extends through all walls of the appendix and whether or not contiguous structures are involved. Thus, an extensive inflammatory process in a retroperitoneally located appendix tends to minimize the chances of roentgenographic clarification. The roentgen findings thus influenced by the position of the appendix and the extent of the inflammatory reaction are also predetermined by the corresponding peritoneal response and the reaction of the bowel and omentum. This highly individual

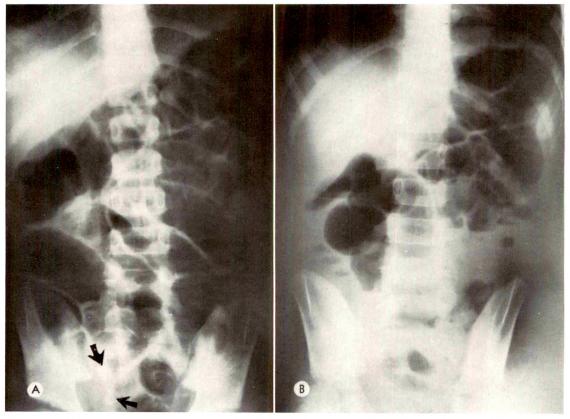


Fig. 12. (A) A supine roentgenogram of the abdomen demonstrates two appendicoliths with associated distended loops of small bowel. (B) Erect roentgenogram of the same patient demonstrates distended loops of small bowel with differential fluid levels consistent with mechanical small bowel obstruction. This is secondary to an appendiceal abscess.

factor is reflected in various degrees in individual patients by the amount of peritoneal transudate and the extent of formation of fibrin, as well as in the secondary reactions resulting in psoas obliteration and reactive lumbar scoliosis. The associated ileus and/or fibrous or fibrinous kink obstruction is a direct corollary of these factors.

In instances of acute localized appendicitis, the roentgen findings on the plain roentgenograms depend on the extent of the inflammatory process and the anatomic position of the appendix. Negative roentgen findings do not rule out the presence of acute nonperforative catarrhal or suppurative disease. The positive findings may be limited to edema of the cecal wall or to the presence of a fluid level in the cecum associated with the dilatation of the

terminal ileum, best detected on horizontalbeam roentgenograms. Fluid filled loops of bowel may be easily missed or confused with neoplastic masses. A small peritoneal transudate or exudate may present as a localized right lower quadrant haziness. The lower one-third of the right psoas density is frequently partially or completely obliterated.

Acute progressive appendictis with extension of the inflammatory process indicates that there is involvement of surrounding viscera and of the parietal peritoneal area without actual abscess formation. The mass which may be visualized in the absence of abscess formation consists of the appendix, the omentum, and the surrounding edematous or adherent bowel. The small bowel may be implicated by the fibrinous exudate which at times produces

matting, kinking, angulation, or adhesions, so that the roentgen picture is that of a small bowel mechanical obstruction. A true small bowel inhibition or paralytic ileus may coexist, offering great difficulty in the differential diagnosis.

In acute appendicitis with localized perforation, the roentgen findings are of two types: those with reference to the inflammatory mass itself and those related to extrinsic contour deformities produced by the mass. Here, all of the signs of acute appendicitis such as "sentinel loop" ileus and obliteration of the psoas density as well as delineation of a soft tissue mass are seen. The mass may be seen to indent and displace the gas filled cecum and/or terminal ileum. Additionally, a localized collection of gas may be present, appearing in the form of single or multiple bubbles.

Pneumoperitoneum in acute appendicitis

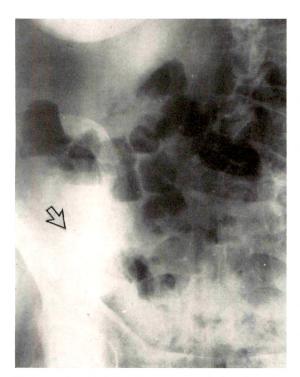


Fig. 13. An erect roentgenogram of the abdomen demonstrates a coprolith in the right lower quadrant. There is an associated soft tissue haziness which is the result of the peri-appendiceal inflammatory reaction. The small bowel dilatation represents an associated localized ileus.



Fig. 14. The 10 minute excretory urogram demonstrates a coprolith that simulated a right ureteral calculus and produced a right hydronephrosis secondary to an appendiceal abscess and periureteral inflammation and edema.

is a rare phenomenon. Frimann-Dahl has not observed pneumoperitoneum in a series of over 2,000 cases. However, pneumoperitoneum may occur in those cases of acute perforation at the appendiceal-cecal junction that are not sufficiently walled off by omentum early in its course. McCort in a review of 648 appendectomies, of which 103 showed perforation, found only 6 cases which demonstrated free air on roentgen examination. In all of these 6 patients,

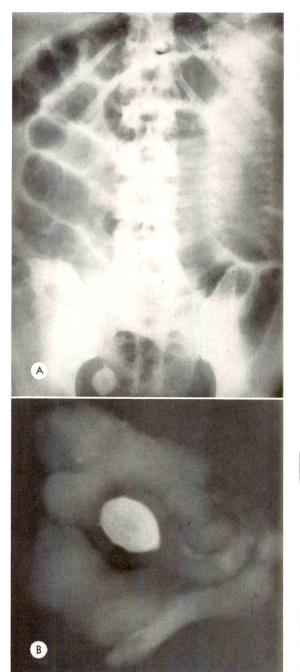


Fig. 15. (A) A supine roentgenogram of the abdomen with a large coprolith containing multiple laminations resembling a gallstone. The associated ileus might easily lead to an erroneous diagnosis of a "gallstone ileus." No gas is visualized in the biliary tree. (Courtesy of Dr. Myron Nobler.) (B) A roentgenogram of the operative specimen demonstrates the calculus to be a coprolith located at the ostium of the appendix.

there was a delay in treatment ranging from 48 hours to 7 days. Steinert *et al.*²⁶ have reported on a single case with pneumoperitoneum due to a basal perforation of the appendix in a series of 98 cases; however, this localized collection of air occurred

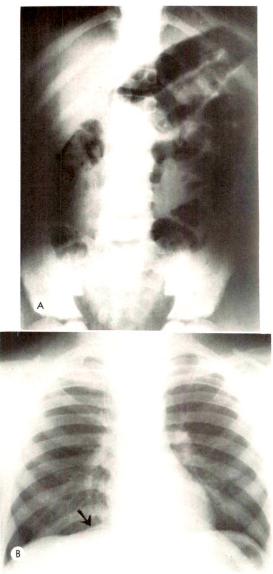


Fig. 16. (A) A supine roentgenogram of the abdomen shows a fairly large coprolith in the right lower quadrant. (Courtesy of Drs. Charles Walkoff and Albert Salzman.) (B) An erect posteroanterior chest roentgenogram of the same patient demonstrates free air beneath the right hemidiaphragm. The pneumoperitoneum was secondary to a perforated appendix associated with a coprolith.

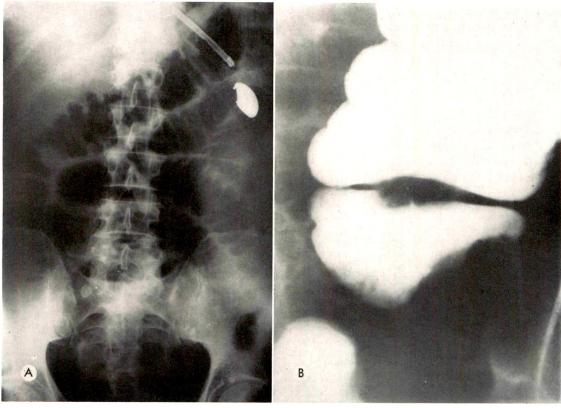


Fig. 17. (A) A supine roentgenogram of the abdomen demonstrates a coprolith in the right lower quadrant with loops of dilated small bowel. The clinical picture was that of mechanical small bowel obstruction. (B) A spot roentgenogram of the cecum during a barium enema examination, performed as an emergency procedure, demonstrates an irregular filling defect in the medial aspect of the cecum produced by an appendiceal abscess.

lateral to the cecum. They saw no case of subdiaphragmatic free air. Obviously, the possibility of such pneumoperitoneum appearing subdiaphragmatically depends on the site of perforation of the appendix and on the availability and degree of development of the omentum as a "sealing-off" organ.25 Likewise, the route of air to the subdiaphragmatic zone must be unimpeded. The fact that the appendiceal perforation is frequently "walled off" and that fibrinous adhesions prevent free access to the subdiaphragmatic space accounts for the relative rarity of pneumoperitoneum as a consequence of appendicitis with basal perforation.

Orally administered barium is not recommended for the diagnosis of acute appendicitis, but Chrom and Gudbjerg³ have dem-

onstrated that the appendiceal lumen is always obliterated in acute appendicitis. Generally, barium enema studies will similarly fail to opacify the inflamed appendix. The differential roentgen diagnosis of chronic appendiceal abscess and cecal cancer or the association of the two requires barium enema examination. If the appendix is visualized, acute inflammatory disease is generally absent.9 Occasionally, the barium will be seen to enter an abscess cavity. The contour defect in the cecum (on the barium enema study) adjacent to an appendiceal abscess is accompanied by increased irritability and inflammatory edema of the mucous membrane with local obliteration of the cecal haustration. Furthermore, contour deformity may involve the cecum, ascending colon, bladder, ileum,

ureter, adnexa, uterus or sigmoid. The finding obviously will depend upon the size and extent of the inflammatory process.

The roentgen findings of acute appendicitis with or without perforation, on plain roentgenograms, can be summarized as follows:

- I. Sentinel loop ileus (gas or fluid filled) in the right lower quadrant. The ileus need not necessarily be localized to the right lower quadrant but may be seen in any quadrant. Horizontal beam roentgenograms may be necessary to demonstrate the gas ileus or the fluid-filled loops.
- 2. Obliteration of the right psoas density, particularly in its lower half (Fig. 18). This finding is occasionally associated with lumbar spine scoliosis.
- 3. A coprolith in the appendix—practically diagnostic of acute (frequently obstructive) appendicitis.
 - 4. Gas bubbles in the right lower quad-



Fig. 18. On this supine roentgenogram of the abdomen, in a patient with acute appendicitis, there is obliteration of the inferior right psoas margin and a fluid collection projected superior to the right ileopectineal line.



Fig. 19. An oblique roentgenogram of the abdomen demonstrates multiple gas bubbles in the right lower quadrant secondary to abscess formation. The abscess was produced by a perforated adenocarcinoma of the appendix.

rant—found with a perforated appendix. Abscess formation is usually present (Fig. 19 and 20).

5. A right lower quadrant soft tissue mass which usually suggests perforation. On at least one occasion we have seen such a finding with acute appendicitis without perforation with secondary omental edema (Fig. 21).

6. Gas in the appendix which may suggest acute appendicitis. On rare occasions, gas may be present normally^{16,22} (Fig. 22 and 23).

The presence of gas in the appendix as a sign of acute appendicitis was first described by Musgrove²⁰ in 1952. Killen and Brooks¹⁶ reviewed the literature in 1965 and reported this finding as indicative of acute appendicitis in 1.9 per cent of 823 patients—a figure arrived at by combining his figures with those of Faegenburg. The sign is not pathognomonic. Samuel²² and we



Fig. 20. On this decubitus roentgenogram of the abdomen of a 22 month old infant, there are multiple gas bubbles in the right upper quadrant secondary to a perforated retrocecal appendix with abscess formation.

have observed this finding in normal individuals. This finding is of value only in association with a corroborative history and physical examination, and especially when associated with appendicoliths.

7. Pneumoperitoneum—a rare finding in appendiceal perforation (Fig. 16 *B*).

8. Fluid in the peritoneal cavity—usually found in acute appendicitis with perforation and generalized peritonitis. The roentgen signs on the plain roentgenograms are well known: obliteration of the preperitoneal fat stripe, a generalized haziness, and an aggregation of small bowel loops in the mid-abdomen.

On barium enema examination, in addition to point tenderness over the appendiceal area during fluoroscopy, the following may be noted:

I. An extrinsic defect involving the cecal

tip, usually indicating perforation and abscess (Fig. 17 B).

2. A soft tissue mass displacing the cecum and right colon.

3. Changes in the terminal ileum suggesting surrounding extrinsic inflammation. These findings include spiculation, irregularity of the small bowel mucosa and irritability. These changes are usually secondary to perforation with abscess formation.

4. Nonopacification on barium enema (or barium meal) studies. On rare occasions this rule does not hold true (Fig. 24).

Another cause of inflammatory disease in the right lower quadrant is tuberculosis. Although the usual site of involvement is the ileocecal area, occasionally the appendix may also be involved (Fig. 25). The incidence of tuberculous appendicitis in tubercular patients has been reported to be as high as 24 per cent. In the general population, the incidence is reported to be between 0.1 to 3 per cent of all specimens

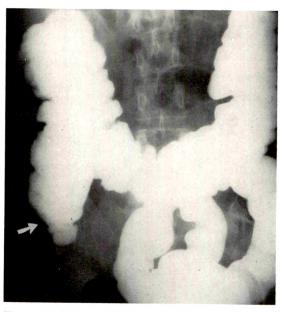


Fig. 21. A barium enema examination reveals a filling defect along the lateral wall of the cecum; the appendix is faintly opacified. At the time of surgical exploration, the appendix was found to be both acutely and chronically inflamed. The filling defect on the lateral margin of the cecum was produced by an omentum which was thickened, inflamed, and adherent to the cecum.



FIG. 22. An anteroposterior roentgenogram of the abdomen in an asymptomatic patient shows a gas filled appendix.





Fig. 24. A barium enema roentgenogram demonstrates a retrocecal appendix filled with barium. At exploration, a perforated appendiceal tip with associated subhepatic abscess was found. This case is highly unusual since the appendix was opacified on a barium enema study—a finding ordinarily considered inconsistent with appendicitis. (Courtesy of Dr. Sol Unger.)

removed, including patients with ileocecal tuberculosis.¹⁹ Isolated cases of tuberculosis of the appendix are rare.

Although diverticulosis of the appendix is sometimes considered congenital, such an entity is actually more apt to be post-

Fig. 23. A gas filled appendix in a patient with acute appendicitis (verified at laparotomy) is shown in this supine roentgenogram of the abdomen.

inflammatory. In the inflammatory type, it is possible that the appendix has undergone perforation during a previous inflammatory episode. This perforated portion then seals with regeneration of mucosa to form an outpouching or diverticulum (Fig. 26). Ochsner²¹ in 1961 found that diverticulosis of the appendix was reported in as high as 60 per cent of patients with acute appendicitis when the operatively removed specimen was examined. Chronic appendicitis was found in 33 per cent of the cases. Twenty per cent of these cases had perforated.

Hultén¹⁴ pointed out that the diverticula which follow perforation are susceptible to reperforation because the underlying disease persists. Consequently, patients presenting with diverticula of the appendix should be either closely observed for signs of inflammatory disease or be considered for prophylactic appendectomies. There is apparently no roentgen method of determining whether or not a diverticulum of the appendix is of the true congenital type or the false acquired inflammatory type.



Fig. 25. An anteroposterior roentgenogram from a barium enema examination demonstrates involvement of the cecum, terminal ileum and appendix by tuberculosis.



Fig. 26. A barium filled pelvic appendix with 3 large diverticula in its distal third is noted in this barium enema examination. (Courtesy of Dr. Sol Unger.)

POSTAPPENDECTOMY DEFORMITIES

The postappendectomy deformities of cecum are well recognized and only a brief reference to them will be made here.

These deformities may be divided into various categories depending on the nature of the surgical procedure performed. The defects may be secondary to inversion of the appendiceal stump without ligation, to deformity secondary to ligation without inversion, and to persistence of part of the organ as a consequence of incomplete subtotal appendectomy. Two of these roentgen abnormalities are illustrated in Figures 27 and 28.

NEOPLASMS OF THE APPENDIX

Neoplasms of the appendix are rarely diagnosed preoperatively. Collins⁴ reports an incidence of carcinoid of 0.5 per cent, of primary adenocarcinoma of 0.08 per cent, and of benign tumors of 4.3 per cent.

The benign tumors (leiomyomas, neuromas, lipomas) are most commonly diagnosed microscopically and are not roent-



Fig. 27. An air contrast spot roentgenogram of the cecum during barium enema examination demonstrates an invaginated, fairly smooth, filling defect which represents an inverted appendiceal stump.

genographically discernible. The most common benign "tumor" of the appendix which lends itself to roentgen diagnosis is the mucocele. These lesions have been reported as occurring in 0.2 per cent of the 50,000 appendices examined by Collins. A mucocele is characterized roentgenographically by its sharp globular smooth contour which may partially invaginate the cecal wall. The wall of the mucocele is occasionally calcified. The differential diagnosis between lipoma, inverted appendiceal stump, appendiceal abscess and carcinoma of the cecum remains a continuous challenge. 6,17,32

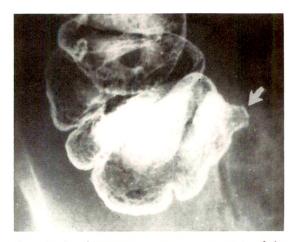


Fig. 28. An air contrast spot roentgenogram of the cecum demonstrates the status after partial appendectomy with a retained patent appendiceal remnant.

A fairly typical roentgen appearance of a mucocele is illustrated in Figure 29.

A malignant neoplasm of the appendix (usually an adenocarcinoma or a malignant carcinoid) is generally discovered on surgical exploration in a patient presenting with perforation, bleeding, obstruction or ascites. Most of these neoplasms originate in the distal one-third of the appendix with obstruction resulting in acute appendicitis, frequently with perforation (Fig. 19). Figure 30 illustrates cecal invasion from a persistent carcinoma of the appendix after appendectomy. Calcification is occasionally observed in carcinoma of the appendix as illustrated in the postmortem specimen in Figure 31, A and B. For the most part, malignant carcinoid, malignant mucocele, and adenocarcinoma of the appendix elude a preoperative diagnosis; 13,28 occasionally, the tumor is so large as to simulate a primary cecal cancer on barium enema study (Fig. 32).

SUMMARY AND CONCLUSIONS

I. Variations in the anatomic positions of the appendix are illustrated, and the importance of recognizing the possibility of these variations and their relationship to

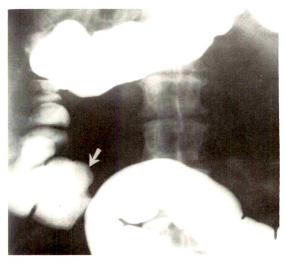


Fig. 29. An anteroposterior roentgenogram during a barium enema examination demonstrates a smooth, rounded, filling defect in the medial wall of the cecum. This is characteristic of a mucocele of the appendix.



Fig. 30. A defect in the cecum secondary to residual appendiceal carcinoma after appendectomy.

the signs and symptoms of the diseases of the appendix is stressed.

2. Hernias containing the appendix are described and illustrated.



Fig. 32. A spot roentgenogram during barium enema examination demonstrates a cecum deformed by a mass which proved to be an adenocarcinoma of the appendix growing into the cecum. The cecal mucosa was intact. (Courtesy of Dr. Harry Z. Mellins.)

3. The findings on the plain roentgenograms of the abdomen in acute nonappendi-

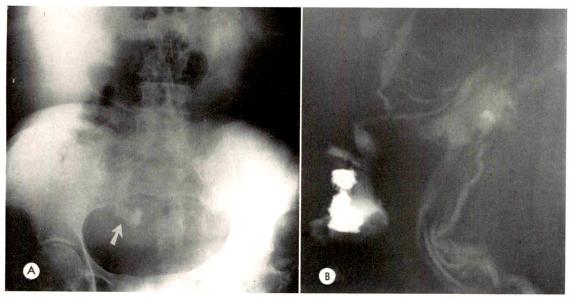


Fig. 31. (A) Calcification in an adenocarcinoma of the appendix is seen on this antemortem supine roent-genogram of the abdomen. (Courtesy of Dr. Harry Z. Mellins.) (B) Roentgenogram of the appendix and ileocecal area at postmortem examination.

- colith and appendicolith inflammatory states of the appendix are stressed and illustrated.
- 4. Postappendectomy deformities are briefly discussed.
- 5. Some benign and malignant tumors of the appendix are described.
- 6. The importance of the role of the radiologist in the diagnosis of the diseases of the appendix, particularly in the inflammatory states, is stressed.

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DIVERTICULITIS OF THE TERMINAL ILEUM*

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CUTE diverticulitis of the terminal A ileum is an extremely rare entity which usually presents with appendicitislike clinical signs. Only 3 cases were found in a review of the literature. The first was reported by Koletsky⁵ in 1941. This was in a 55 year old man who showed typical symptoms and signs of appendiceal perforation with abscess formation. At operation, an abscess in the right lower quadrant was found and drained. The patient subsequently died and at autopsy was found to have a necrotic diverticulum of the terminal ileum, 1.5 cm. from the ileocecal valve. There was a large abscess cavity in the right lower quadrant. Diverticula were also found in the cecum and ascending colon.

The second case was reported by Walker. This patient was a 53 year old woman who presented with typical clinical findings of acute appendicitis. She had had mild indigestion and diarrhea for several months. At operation, a short inflamed segment of terminal ileum, about 7 cm. from the cecum, was found and excised. The specimen revealed an ileal diverticulum between the layers of the mesentery, measuring about 1 cm. in diameter. It contained a fecal concretion and was surrounded by pus.

In 1958, Lee and Finby⁶ reported the third case. The patient was a 51 year old man with a rigid right abdomen, bloody diarrhea, and sepsis. At operation, there was thought to be a carcinoma of the terminal ileum. The affected ileum was resected and an ileotransverse colostomy performed. Dissection of the specimen revealed an abscess cavity originating from a small diverticulum on the mesenteric side of the terminal ileum. It had perforated into the mesentery and eroded a branch of

the right ileocolic artery. No other diverticula were found. The patient made an uneventful recovery.

None of these 3 cases had had barium enema studies. The following case is the first in which the correct preoperative diagnosis has been made by barium enema examination and small bowel series, providing unequivocal, if delayed, roentgen evidence of this entity.

REPORT OF A CASE

M.H., a 78 year old Negro woman, was admitted to the Cincinnati General Hospital for the first time on November 16, 1964. She had been in good health until 5 months earlier when she first noted episodes of intermittent sharp right lower quadrant and right flank pain unrelated to food intake. There was occasional radiation of the pain to the back and right shoulder. These episodes occurred 2 to 3 times per day and were associated with mild nausea but no vomiting. There had been no change of bowel habits, melena, or gross blood in the stool. The patient had taken laxatives for 3 or 4 years for constipation. Past history revealed that she had had typhoid fever as a child and mild hypertension for 20 years.

A barium enema examination, performed on October 17, 1964, while she was an outpatient, revealed a 3 cm. long defect in the ileum several inches proximal to the ileocecal valve (Fig. 1A). The involved segment impinged on an adjacent, more proximal segment of ileum and indented it. Six days later, a small bowel examination again revealed the intrinsically involved segment, but now the defect appeared shallower and eccentric (Fig. 1B). The mucosa in the region of the defect appeared swollen but not destroyed. The adjacent indented segment was no longer identified. The remainder of the gastrointestinal tract, an oral cholecystogram, and an intravenous pyelogram were all normal. The patient's symptoms gradually worsened and she was referred to the hospital for further evaluation.

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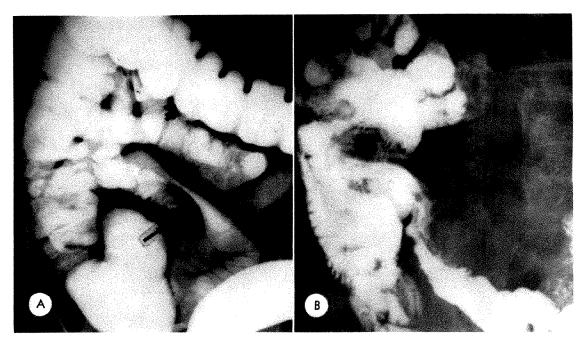


Fig. 1. (A) Barium enema study showing a defect in the ileum (arrow). There is impingement on an adjacent ileal segment. (B) Small bowel examination, 6 days later, again shows the intrinsically involved segment. The neck of one of the diverticula can be seen.

On admission, the temperature was 98.8°F., pulse 88, respiration 20, and blood pressure 180/100. Pertinent physical findings were confined to the abdomen. There was generalized tenderness without rebound, most marked in the right lower quadrant. Bowel sounds were within normal limits. No masses or organs were palpable. The rectal and pelvic examinations were normal.

The leukocyte count was 6,000 and the hematocrit 37 per cent. Urinalysis was normal. A variety of blood chemistry examinations was normal. A 5-hydroxyindoleacetic acid test on the urine was normal. The electrocardiogram suggested anterior myocardial ischemia. Multiple stool guaiac tests were negative.

On November 18, the small bowel examination was repeated and revealed two narrownecked diverticula at the site of the defect, which now appeared smaller. In retrospect, the neck of one of the diverticula was identified on the roentgenograms of the first small bowel examination (Fig. 1B). A diagnosis of diverticulitis was now made. Follow-up small bowel examination on December 3, almost 2 months after the initial demonstration of the lesion, again showed the 2 diverticula but only a questionable defect (Fig. 2, \mathcal{A} and \mathcal{B}).

The patient was treated with antibiotics and her symptoms improved. On January 7, 1965, a laparotomy was performed. Two small, firm, irregular, barium-containing diverticula were found extending between the leaves of the mesentery of the terminal ileum, 2 inches from the ileocecal valve. There was no evidence of an abscess. A right ileocolectomy with ileotransverse colostomy was performed. The postoperative course was uneventful. The pathologic specimen (Fig. 3) revealed diverticulosis with chronic diverticulitis. The appendix and colon were normal.

DISCUSSION

The first roentgenographic demonstration of small bowel diverticula beyond the duodenum was presented by Case³ to the American Roentgen Ray Society in 1915. Since that time, many additional articles on this topic have been published. In most reports, jejunal and ileal diverticula have been grouped together and duodenal diverticula excluded, as in the present discussion. The incidence of jejuno-ileal diverticula ranges between 0.3 and 0.5 per cent^{8,10} of small bowel examinations. Our own experi-

ence is in the area of the latter figure. Of interest is the frequent association with diverticula of the duodenum (44 per cent) and of the colon (24 per cent), and with hiatus hernia (20 per cent).¹⁰

As a rule, small intestinal diverticula are multiple and usually confined to the jejunum. The ratio of jejunal to ileal diverticula is said to be almost 5:1. 1.6 In the individual case, ileal diverticula are seldom numerous. In the past 2 months, we have seen 3 more examples of diverticula of the terminal ileum (Fig. 4, A and B). In 1, there were no diverticula demonstrated elsewhere in the small intestine.

Diverticulum of the small intestine is usually acquired rather than congenital. It is a "false" diverticulum, consisting of a thin-walled sac rimmed by mucosa, submucosa, and peritoneum. The muscular coat is thin or absent. The herniation of mucosa and submucosa through the muscularis occurs on the mesenteric border of the intestine, commonly at the site of vascular penetration from the mesentery. 6,12

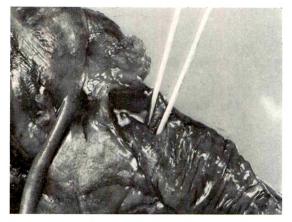


Fig. 3. Resected terminal ileum, cecum, and appendix. A wooden probe has been placed into the mucosal opening of each of the diverticula. The appendix and unopened cecum are to the left.

Most ileal diverticula are found quite near the ileocecal valve. They are readily distinguished from Meckel's diverticulum, which is larger, solitary, and arises on the *antimesenteric* side of the ileum, 30 to 90 cm. proximal to the ileocecal valve. Unlike its jejunal counterpart, the ileal diverticulum is generally quite small and

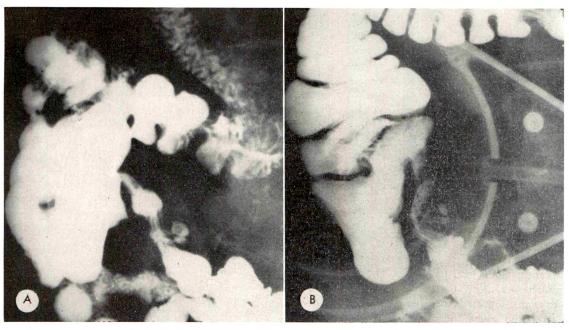


Fig. 2. (A and B) Small bowel examination about 2 months after Figure 1 A.

Two diverticula are now apparent.

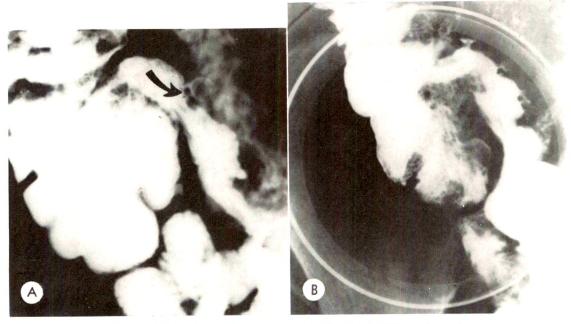


Fig. 4. (A) A diverticulum is present in the terminal ileum (arrow). (B) Multiple terminal ileum diverticula in another patient.

has a narrow neck. 11 In these respects, it more closely resembles a colonic diverticulum.

Complications of small intestinal diverticulosis are relatively infrequent. Of these, acute diverticulitis is one of the most common and, as might be expected, its incidence is much higher with jejunal diverticula. Other complications include intestinal obstruction, volvulus, intussusception, concretion formation, free perforation, fistula formation, spontaneous pneumoperitoneum, neoplasm, hemorrhage, hypochromic anemia, and macrocytic anemia with or without sprue-like symptoms.^{2,6,9}

The inflammatory changes of diverticulitis are probably the result of irritation or occlusion of the diverticulum by food particles or a foreign body. Edema and local swelling cause further stasis. The inflammation tends to extend intramurally but perforation may supervene with the formation of either a localized or generalized peritonitis. Perhaps, as Fleischner *et al.*⁴ have suggested in relation to colon diverticulitis, small intestinal diverticulitis is the result of intramural perforation. It should be noted

that peritonitis and inflammation of the mesentery may occur without any gross changes in the lining of the involved diverticulum or in the adjacent intestinal mucosa. When the inflammatory process subsides, areas of fibrosis may cause partial intestinal stenosis or complete obstruction. O

There are no characteristic signs or symptoms of diverticulitis of the small bowel. Recurrent bouts of pain and tenderness with intervening periods of freedom from pain have been noted in some cases. The pain ranges from mild to disabling. Abdominal rigidity and palpable mass may be present.^{2,9} Fever and elevated leukocyte count may occur. The need for prompt surgical intervention is often apparent even though the correct diagnosis is not considered.

Diverticulitis may present on contrast studies as an extrinsic mass contiguous with and indenting the small bowel; as a local thickening of the mucosal folds in the affected segment; or as a perforation, localized or free. In an unreported case of terminal ileum diverticulitis shown us by

Dr. P. D. Meyer, of Columbus, the associated mass produced a large extrinsic defect on the inferomedial aspect of the cecum. Visualization of a diverticulum in the vicinity of the small intestinal lesion is essentially diagnostic. As in the present case, the diverticulum may escape detection if the barium study is made during the active inflammatory phase because of compression of its neck by the inflammatory process.

Undoubtedly, most cases of diverticulitis of the terminal ileum will continue to be operated on under the mistaken diagnosis of acute appendicitis, without contrast studies. However, not all cases present in this manner, so that awareness of the roentgen manifestations of this entity may, at times, assume importance.

SUMMARY

Diverticulitis of the terminal ileum is a rare entity which is usually discovered at operation for suspected acute appendicitis. A case is reported in which the inflammatory process was less acute and barium studies led to a correct preoperative diagnosis. The subject of jejuno-ileal diverticulosis is discussed and the clinical and roentgen manifestations of diverticulitis are described.

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DUODENAL TUBERCULOSIS

REPORT OF A CASE

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TUBERCULOSIS is a protean disease which can be readily confused with many other benign and malignant processes. This fact is well worth keeping in mind, especially in regions where other bacterial and parasitic diseases are endemic, such as Salvador (Bahia, Brazil).

In the statistics of the Department of Health of the State of Bahia, tuberculosis ranks first among the causes of death.³

Duodenal tuberculosis is extremely rare. Brown and Sampson,1 in 184 autopsied cases of pulmonary tuberculosis with intestinal lesions, found lesions restricted to the small intestine in 6 per cent of the cases and to the large intestine in 19 per cent. In the remaining 75 per cent of the cases, there were lesions in the ileum and cecum. They did not refer, however, to lesions in the duodenum. Matthews et al.6 mention 105 cases of generalized intestinal tuberculosis and report 18 cases of localized duodenal tuberculosis with only 6 of these histologically confirmed. Granet,5 in 1935, in 29 autopsied cases of tuberculosis enteritis, found 4 with ulcerations in the duodenum. Buckstein,2 in 1953, cited a case of hyperplastic tuberculosis of the first portion of the duodenum. In 1957, Feldman4 found that duodenal tuberculosis occurred in only 0.5 per cent of the cases of tuberculosis autopsied. Wig et al.7 in 67 cases of abdominal tuberculosis, found 49 of a hyperplastic type. In 60 cases which had small bowel roentgenograms, there was no evidence of duodenal involvement.

In the reviewed Brazilian literature, no references to duodenal tuberculosis were found.

REPORT OF A CASE

M.B.S., a 43 year old female, mulatto domestic from the interior of Bahia came to the Hospital Aristides Maltez Out Patient Department for the first time on February, 5, 1962, complaining of pain in the right upper quadrant of 8 months' duration. This pain had a sudden onset, radiated to the sternum and disappeared spontaneously. The general state of the patient was poor. The mucous membranes were pale and there were signs of marked weight loss. There was diffuse tenderness of the abdomen. The liver was palpable, had rounded edges and was tender to palpation. The patient did not return to the hospital for the necessary laboratory examinations. On December 11, 1962, the patient was admitted to the Hospital das Clínicas with similar complaints plus diarrhea of 10 days' duration and semiliquid stools without blood or tenesmus. The past history was negative for chest disease, syphilis and rheumatism. There was no history of previous hospitalization. The only symptoms were anorexia and asthenia. There were no respiratory complaints. Before the onset of diarrhea, her bowel habits were normal. Her weight was 27 kg. The examination of the chest was negative. The abdomen was diffusely tender. The liver and spleen were not palpable.

Laboratory examinations showed iron deficiency anemia, and low serum proteins with a normal A/G ratio. The cephalin flocculation test was negative. Chest roentgenograms showed pleural thickening in the outer region of the inferior half of the right lung. There was no active lung lesion. In the upper gastrointestinal series, the stomach and duodenal cap were normal. The duodenal arch was hypotonic and the mucosal pattern was irregular. The patient received supportive treatment only and was discharged 16 days later.

On January 30, 1963, the patient was ad-

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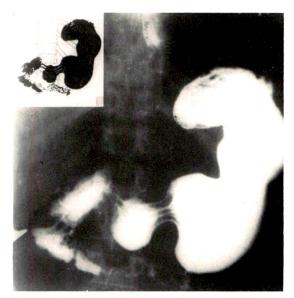


Fig. 1. Roentgenogram showing irregularity of the mucosal pattern of the third and fourth portions of the duodenum and stasis in the second portion.

mitted to the Hospital Aristides Maltez. She was severely ill and complained of the same symptoms as previously. Palpation of the abdomen revealed a tender and hard epigastric mass. The liver was palpable and had a nodular surface. Because of a presumptive diagnosis of a

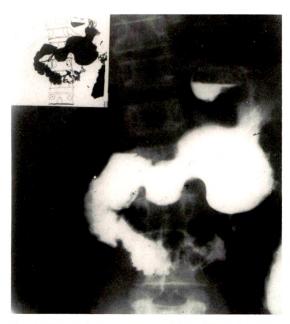


Fig. 2. The lesions are more evident. Note the sharp limits between the diseased segment and the neighboring segments.



Fig. 3. In the supine roentgenogram, the extension of the lesion, involving the third and fourth portion of the duodenum and reaching the angle of Treitz, is demonstrated.

malignant tumor of the stomach, roentgenograms of the chest and an upper gastrointestinal series were made (Fig. 1 through 4). The latter showed stasis of the barium meal at the third portion of the duodenum which demonstrated irregular filling defects with intraluminar vege-

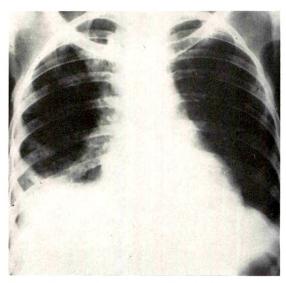


Fig. 4. Roentgenogram showing the disseminated nodules in the lower two-thirds of both lungs and pleural thickening on the right.



Fig. 5. Photomicrograph of duodenal lesion. Extensive area of caseation necrosis in the submucosa, surrounded by infiltration of lymphocytes and histocytes (H & E×17).

tations. The first and second portions of the duodenum were dilated. The roentgenograms suggested a malignant tumor or a granulomatous inflammatory process. The chest roentgenograms showed diffuse nodular shadows in the inferior two-thirds of both lungs and pleural thickening in the right base. Her diarrhea became much worse and was unresponsive to treatment with nonabsorbable sulfa drugs. Seven days after admission she developed severe dyspnea and lapsed into a coma from which she did not recover.

Autopsy Report (Fig. 5 and 6). Autopsy revealed a severely emaciated, dehydrated cadaver, with a slightly protruded abdomen, but without noticeable tumors. There was cyanosis of the upper extremities and edema of the legs. There were pleural effusion and adhesions on

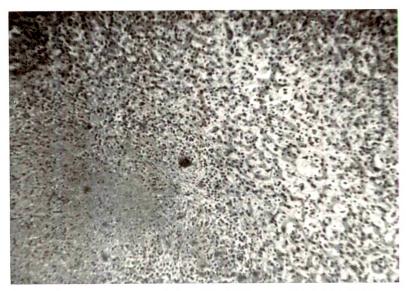


Fig. 6. Photomicrograph of liver. Granulomatous lesion identical to that in the duodenum (H & E×80).

the right (240 ml.) There was miliary dissemination of tuberculosis in the pleura, peritoneum and on the loops of the small bowel. The mesenteric lymph nodes were enlarged, with caseation necrosis. The liver was 4 cm. below the costal margin. There was miliary tuberculosis of the lungs, liver, pancreas, spleen and left kidney. The stomach was normal. In the third and fourth portions of the duodenum, near the angle of Treitz, there was an annular ulceration of mucosa, measuring 4 cm. in diameter, with raised and irregular edges and a yellowish granular bottom. On cutting, a thickening of the wall was noticed at this point with patchy yellowish areas of indefinite contours. The rest of the duodenal mucosa was edematous but not ulcerated. In the terminal ileum, 12 cm. above the ileocecal valve, there was a second ulceration, I cm. wide, involving the entire circumference of the organ. Similar ulcerations were also observed in the cecum and descending

Microscopic examination of the duodenum, terminal ileum, cecum and descending colon showed extensive areas of caseation necrosis surrounded by epithelioid cells, lymphocytes and giant cells. The lesions were noted mainly in the submucosa, although the precise location in the ulcerated regions could not be ascertained.

DISCUSSION

Intestinal tuberculosis can be classified as primary or secondary to dissemination of a lung lesion. In view of the pathologic findings, the reported case can be considered as a primary lesion of the intestine with posterior multivisceral miliary dissemination. Usually, the intestinal lesions of tuberculosis are associated with other advanced systemic lesions. Isolated forms of intestinal tuberculosis, particularly of the duodenum, are extremely rare. The ileum and cecum are more vulnerable sites. In the literature, the following clinical forms are described: ulcerative, hyperplastic and infiltrative. Feldman⁴ added an additional form, enteroperitoneal, where there is involvement of the peritoneum, lymph nodes and mesentery. The most common form is the ulcerative one.

SUMMARY

A case of duodenal tuberculosis which simulated a malignant tumor is reported. The patient was a 43 year old female mulatto with diffuse abdominal pain, tumor in the epigastric region and nodules on the surface of the liver. The roentgenograms showed an ulcerative and hypoplastic lesion at the third and fourth portion of the duodenum. In the lungs were multiple nodular shadows simulating carcinomatous dissemination.

The differential diagnosis is discussed from a roentgenologic point of view.

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THE ROENTGENOGRAPHIC FINDINGS IN 3 CASES OF TERMINATION OF THE COMMON BILE DUCT IN DUODENAL DIVERTICULA*

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IN 1911, Baldwin¹ reported 4 cases in which the common bile duct terminated in a duodenal diverticulum. All of these cases were found at postmortem examination. Collett, Tirman and Caylor³ were the first to report a case diagnosed roentgenographically by a postoperative cholangiogram and upper gastrointestinal series in 1950. Munk,¹ in 1959, reported the diagnosis for the first time by intravenous cholangiography. We have been able to find reports of 33 cases of this anomaly to date.

After a review of all the available anatomic reports, Munk⁷ found that the walls of the diverticula contained all layers of the duodenum including the muscularis. The opening of the common duct into a diverticulum may be of importance in the etiology of biliary and pancreatic disease because of 2 factors: (I) the retention of contents in the diverticulum for long periods of time, and (2) the incompetence of the sphincter of Oddi, which has been found to be more common in cases when the ampulla of Vater is situated within the diverticular wall than under normal anatomic conditions.

The roentgenographic demonstration of this anomaly has been made most commonly from operative and postoperative choledochograms, frequently combined with an upper gastrointestinal study. Several cases⁷ have been reported in which barium was seen passing from a diverticulum into the common bile duct. Air within the biliary tract has also been noted. This might be expected since incompetence of the sphincter of Oddi occurs more frequently in this anomaly than normally. Doermann and Means⁴ reported a case

recently in which they were able to visualize a filling defect in the diverticulum, representing the abnormally placed choledochal termination, during a gastrointestinal study. Intravenous cholangiography appears to be the best method by which this anomaly can be shown preoperatively. The filling of a duodenal diverticulum is not proof that the anomaly exists; it is necessary to visualize the common duct entering the diverticulum. Obviously, operative and postoperative cholangiographies will accomplish this most satisfactorily.

REPORT OF CASES

Case I. Mrs. E.B. (B.G.H. No. B-12922), a 45 year old female, was admitted to the hospital on December 26, 1959. In 1936 a posterior gastroenterostomy was performed for a peptic ulcer. She was asymptomatic until 5 months prior to this admission when she developed abdominal pain and cramps. These symptoms have been recurrent. She had an episode of melena in early December.

Physical examination revealed some epigastric and right upper quadrant tenderness. Laboratory work revealed a normal hemoglobin level; stools were negative for blood.

Roentgenographic studies prior to admission had demonstrated the gastroenterostomy to be functioning. There was a duodenal diverticulum arising from the posterolateral aspect of the upper part of the second portion of the duodenum. This had a neck about 1.5 cm. in diameter and the diverticulum itself varied in diameter from 4 to 6 cm., the size depending on the degree of distention. The diverticulum pointed superiorly in relation to its duodenal attachment (Fig. 1).

At surgery, the duodenal diverticulum was found lying lateral to the duodenum in retroperitoneal tissues, in approximation to the

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Fig. 1. Case 1. Roentgenogram demonstrates the position of the duodenal diverticulum as described in the text.

right kidney. This was dissected free, and it was observed that the common duct entered the diverticulum from posteriorly at 2 o'clock.

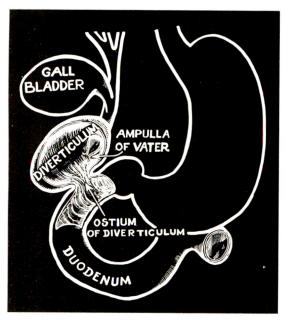


Fig. 2. Case I. Diagram of the surgical findings.

The diverticulum opened into the duodenum at 4:30 o'clock (Fig. 2). A portion of the diverticulum was resected. The common duct was transected at its entrance into the diverticulum. The remainder of the diverticulum was inverted into the duodenum and closure of the duodenal defect was carried out. Then the common duct was re-implanted in the superior surface of the junction of the first and second portion of the duodenum. The gallbladder was removed and a T-tube was placed in the common duct.

Pathologic examination showed the excised sac to be 5.5 cm. at its widest diameter. The inner lining was intestinal mucosa. The wall was 0.2 cm. thick. Histologic study revealed the wall to consist of duodenal mucosa with Brunner's glands. Underneath the mucosa, the subserosal fat tissues showed moderate congestion.



Fig. 3. Case I. Postoperative cholangingram demonstrating the anastomosis between the common duct and the second portion of the duodenum. The contrast medium also outlines the invaginated portion of the diverticulum.

The patient's postoperative course was uneventful. Cholangiography was done on the tenth postoperative day through the T-tube which had been placed in the common duct at surgery. This showed free communication to the duodenum through the anastomosed common duct. The intraluminal contrast material in the duodenum outlined the portion of the diverticulum which was inverted (Fig. 3). The patient was discharged and has had no return of abdominal complaints.

Case II. Mrs. M.Z. (B.G.H. No. 307363), a 57 year old female, was admitted to the hospital on February 5, 1963. In August, 1958, she was admitted to another hospital because of upper abdominal complaints and a cholecystostomy was performed. Her symptoms persisted, and in July, 1959, she was readmitted to the same hospital and a cholecys-

tectomy was carried out. Since that time she has had repeated attacks of epigastric and right upper quadrant pain. There has been no jaundice.

Physical examination was not remarkable. An intravenous cholangiogram did not give satisfactory visualization of the biliary ducts.

On February 12, 1963, the patient was operated on. Common duct exploration revealed 3 large and 6 small stones which were removed. The ampulla of Vater was dilated. An elongated cystic duct stump was removed. A T-tube was inserted in the common duct and cholangiography was done. A dilated common duct and hepatic ducts were noted and a small amount of contrast material was thought to enter the duodenum.

The patient's postoperative course was benign, and on February 21, 1963, cholangiography was done through the T-tube (Fig. 4,

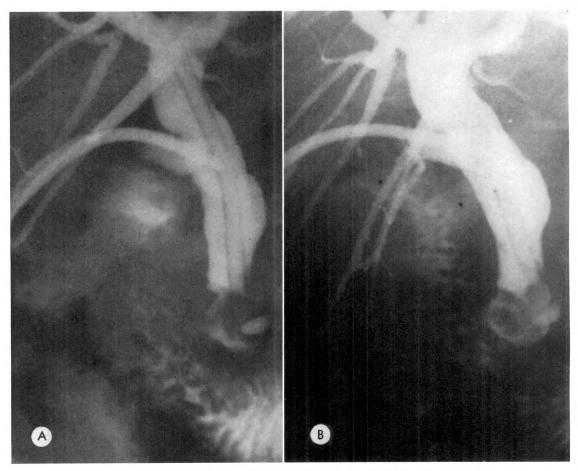


Fig. 4. Case II. (A and B) Postoperative cholangingrams showing the dilated common duct entering the duodenal diverticulum. Note the common entrance with the pancreatic duct.

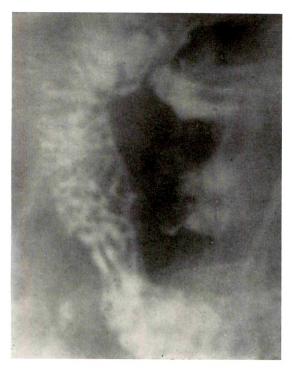


Fig. 5. Case II. Spot roentgenogram of the duodenal sweep with oral contrast material, which also outlines the diverticulum.

A and B). Contrast material outlined a dilated common duct which entered a diverticulum about 2 cm. in diameter. A short segment of the pancreatic duct was outlined which had a common entrance with the common duct into this diverticulum. The diverticulum entered the duodenum at the medial aspect of the lower segment of the second portion of the duodenum. The neck of the diverticulum measured about 1 cm. across.

On review of the operative cholangiogram, it was obvious that the small amount of contrast material which was thought to be in the duodenum was actually in the diverticulum.

On February 23, 1963, after removal of the T-tube, a contrast study of the upper gastro-intestinal tract was carried out. The duodenal diverticulum was visualized, but no contrast material could be refluxed into the common or the pancreatic duct (Fig. 5).

The patient was discharged that afternoon without complaints.

CASE III. Mr. V.B. (B.G.H. No. 355084), a 57 year old white male, was admitted to the hospital on May 16, 1964. The patient was a

mild diabetic. He had had an attack of upper abdominal distress with chills, fever and jaundice on April 15, 1964. Physical examination revealed a slightly obese, white male with no pertinent physical findings. The jaundice had cleared at the time of admission.

Laboratory work was normal.

Roentgenographic studies carried out outside the hospital prior to admission were reported to show a normal upper gastrointestinal tract and cholelithiasis.

At surgery, the gallbladder was found to contain multiple calculi. A catheter was inserted through the cystic duct and operative cholangiography was carried out. This revealed a stone at the ampulla and almost complete obstruction. The common duct measured approximately 1.2 cm. in diameter and the wall

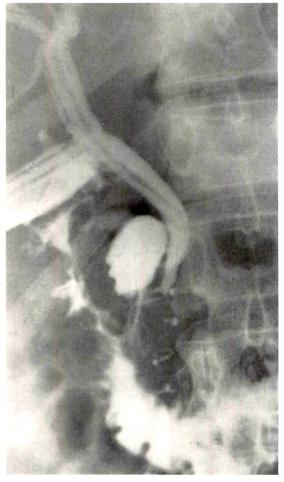


Fig. 6. Case III. Postoperative cholangingram showing the termination of the common duct in the neck of the diverticulum.

was somewhat thickened. The gallbladder was removed and the common duct was opened and explored. No calculi were found proximally and a complete obstruction was found distally. It was impossible to dislodge the distal stone, so the duodenum was opened in a transverse manner over the stone. Upon opening the duodenum, the stone could not be seen but could be felt. Using a stone grasping forceps within the common duct and finger pressure within the duodenum, the stone was broken up and removed in fragments.

It was noted that there was a duodenal diverticulum immediately adjacent to the ampulla of Vater and since the ampulla was never visualized, it was felt that the ampulla emptied into the duodenal diverticulum. A T-tube was placed in the common duct and the abdomen was closed.

Pathologic examination of the resected gallbladder showed moderate chronic cholecystitis and cholelithiasis.

Postoperatively, T-tube cholangiography



Fig. 7. Case III. Oral contrast material visualized the duodenal diverticulum without any reflux into the common bile duct.

was done. The common duct was of normal caliber and terminated in the neck of a duodenal diverticulum. The ampulla of Vater was located about 2 cm. above the junction of the diverticulum with the duodenum (Fig. 6). Oral barium study demonstrated the duodenal diverticulum (Fig. 7). No contrast medium could be refluxed into the common bile duct.

SUMMARY

One of the rare anomalies of the biliary tract is the termination of the common bile duct in a duodenal diverticulum. Three cases are reported here to add to the 33 previously described.

Contrary to comments in the literature, no reflux of contrast material from diverticulum into the common bile duct could be demonstrated in any of our cases.

In 2 of our cases, the common duct terminated in the neck of the diverticulum and in the third at the fundus.

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DIVERTICULA AND DUPLICATIONS (ENTEROGENOUS CYSTS) OF THE STOMACH AND DUODENUM*

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IVERTICULA and duplications (enterogenous cysts) constitute a roentgenologically heterogenous group of malformations, some varieties of which are only occasionally seen in the stomach and duodenum. Although there is considerable evidence in support of a common etiology, 44 none of the theories advanced provides an acceptable explanation of the etiology in the cases studied so far.28 The wide diversity of opinions is reflected in the multitude of terms used in the literature to describe these lesions.20 The terms used in this paper are the most common ones. They represent different extremes within the group.

Numerous papers have been published on the clinical and therapeutic aspects of these malformations. Nevertheless, surprisingly little is still actually known about them, mainly, perhaps, because the reported series have been too small to permit any valid conclusions.

Accounts of the roentgenologic features are few and mainly restricted to occasional case reports. In the textbooks^{6,14,37,40} simple diverticula are discussed quite thoroughly, but intraluminal diverticula and duplications, *i.e.*, malformations belonging to the same group, are mentioned only in passing or completely ignored.

The aim of the authors is to use some well known roentgenologic features as a basis for discussion of the more unusual findings in these lesions.

ROENTGENOLOGIC FINDINGS AND
DIAGNOSTIC CONSIDERATIONS
DIVERTICULA OF STOMACH AND DUODENUM

The roentgenologic findings in diverticula of the stomach and duodenum are

generally typical: a sac-like outpouching of the wall with an even, often rounded contour and a narrow neck. However, in routine examinations, the diverticula may be incompletely filled by the contrast medium and then easily overlooked. This is particularly applicable to cases of juxtacardiac diverticula in the stomach. The observation of a fluid level capped by air on roentgenograms made by using a horizontal beam provides the clue (Fig. 1A). In most cases the findings on roentgenograms made in suitable projections then become diagnostic (Fig. 1B). It should be noted that some diverticula are not consistently outlined on repeat studies. Whether this is due to gross pathologic changes or functional disturbances is not known. Only in exceptional cases can ulcerations or other mucosal changes in the diverticula be visualized on roentgenograms.

Some rather uncommon gastric diverticula show a different roentgen appearance. The neck and the sac-like bulge in the wall are less prominent or almost absent. Macroscopically, these malformations appear as depressions in the wall surrounded by heaped up masses of tissues. Roentgenologically, these diverticula produce even, usually rounded, filling defects seen en face as halos about the contrast filled depression in the wall. It is impossible to differentiate them from ulcerating mesenchymal tumors or an accessory pancreas (Fig. 2, \mathcal{A} , \mathcal{B} and \mathcal{C}).

All of the intraluminal diverticula described thus far have been situated in the duodenum.³¹ Although these malformations are very rare, their roentgenologic appearance is so typical that they do not present any problems of diagnosis (Fig. 3,

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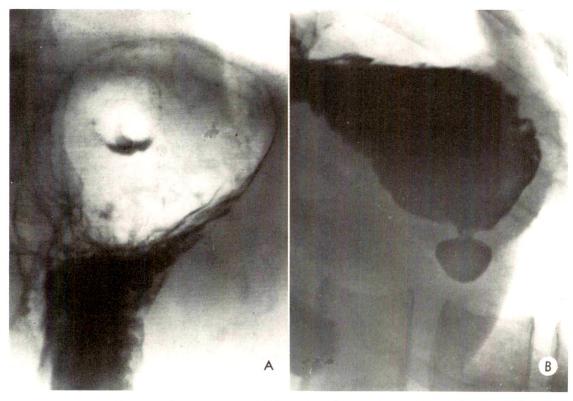


Fig. 1. (A) Juxtacardiac diverticulum on the posterior wall of the fornix. Standing position. Small fluid level in the diverticulum capped by air. (B) Supine position, horizontal beam. The diverticulum is now filled with contrast medium.

A and B). The diverticular sac, which usually begins at the level of the duodenal papilla or immediately proximal to it, extends in a distal direction. On contrast studies, the wall of the diverticulum is visualized as an even, thin radiolucent stripe. Fluoroscopy shows contrast medium passing in and out of the diverticulum as the diverticulum changes size and shape with peristalsis. The mucosal pattern can be demonstrated when the proper amount of contrast medium has been given and adequate compression on the abdomen has been applied. With more massive filling, the diverticulum can be expanded to the degree where it constitutes a relative obstruction. The diverticular sac cannot be projected away from the duodenum. When there is difficulty in the evacuation of the contents from the diverticulum, the roentgenologic appearance may resemble an arteriomesenteric occlusion or an intramural hemorrhage.

DUPLICATIONS OF STOMACH AND DUODENUM

Roentgen observations in duplications are dependent on the location and size of the malformation and on the presence of an open communication with the functioning portion of the gastrointestinal tract. Since most duplications lack this communication, they appear as space-occupying lesions (Fig. 4) causing varying degrees of deformity, narrowing and displacement of the adjacent organ.

When this type of deformity is found in a child, one should consider the possibility of duplication. A gastric tumor is not frequently found in children;³⁰ however, various extragastric expansive processes must be considered.^{4,6} The possibility of the

lesion being due to a true neoplasm increases with age.

Calcification in the area may be of diagnostic significance. To our knowledge, it has never been described in duplications, but it has been observed in malignant⁹ and benign¹⁹ gastric tumors and in many extragastric neoplastic lesions.^{4,6} Calcification within the pancreas frequently has a characteristic distribution and appearance and generally points to a past history of pancreatitis.²

Dilatation of the duodenal loop may be present with duplications⁶ and also in benign and malignant processes in the head of the pancreas.²² In either condition the distance between the spinal column and

the stomach may be increased.

Roentgenograms showing deformity, narrowing or displacement of the stomach or duodenum, *i.e.*, findings similar to those noted with duplications, are sometimes seen following abdominal trauma or in patients treated with anticoagulants. This is due to an intramural hematoma, which is usually absorbed fairly rapidly.

Unlike intra-abdominal gastric duplications, intrathoracic duplications are frequently noted to be combined with vertebral defects. The presence of both, a posterior mediastinal mass and a vertebral defect, should therefore raise the suspicion of the gastric duplication.

The picture may be even more confusing

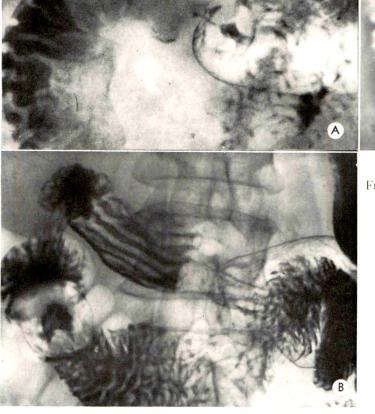




Fig. 2. (A) Diverticulum in the posterior wall of the pyloric antrum close to the minor side (biopsy).

(B) Poorly differentiated, probably myogenic tumor in the second portion of the duodenum (biopsy).

(C) Accessory pancreas on the lesser curvature side of the pyloric canal (biopsy). In all these cases, the lesion appears as a rather well-defined halo-like defect in the contrast material about a central, somewhat irregular deposit of contrast medium. Roentgenologic differentiation is impossible.

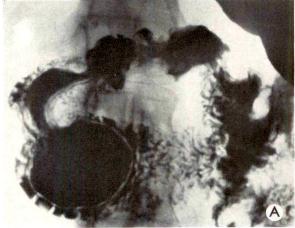


Fig. 3. (A) Intraluminal diverticulum. The orifice of the diverticulum is situated near the duodenal papilla. The wall of the diverticulum appears as a radiolucent stripe surrounded by positive contrast medium. Prone position. (B) Lateral view, vertical beam.

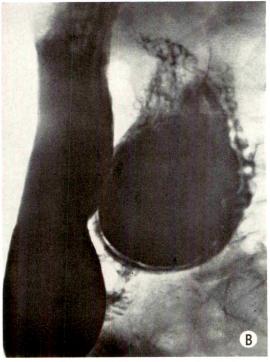




Fig. 4. Gastric duplication (biopsy). Large, somewhat diffusely outlined filling defect in the body of the stomach. This is caused by the duplication issuing from the posterior wall of the stomach. No communication with the functioning part of the gastrointestinal tract.

in cases of duplication with a free communication with the functioning part of the gastrointestinal tube. The communication may vary in length and caliber. In uncomplicated cases, it presents a regular outline with normal mucosa. If the communication is wide, food and contrast medium pass easily between the stomach or the duodenum and the duplication. Roentgen examination in these cases may yield rather bizarre findings, i.e., large, irregular, partially contrast filled cavities containing food remnants. Retention in the duplication may, in turn, give rise to an inflammatory process. False diverticula due to penetrating ulcers or ulcerating tumors may be difficult to distinguish from this type of duplication. A case of strangulated Richter's hernia with a similar appearance has recently been described.5

DISCUSSION AND SUMMARY

Diverticula are relatively rarely found in the stomach.^{18,42} They are somewhat more common in the duodenum.^{3,21} In spite of the fact that most of these seem to be congenital malformations, they are almost never found in children. 6.14,33,34 Although generally asymptomatic, some patients have complaints of intermittent abdominal pains. Typically, the pain increases in intensity in certain positions, such as the patient lying down after eating.11,35,36,42 In other cases the symptoms are similar to those found with peptic ulcer or gallbladder disease. 11,16,26,32,35,36 These latter diseases are frequently associated with diverticula and should receive appropriate treatment. The diverticulum may be responsible for the symptoms if no other cause can be found. Our knowledge of these malformations is still incomplete in many respects, and only studies of large series can provide definite answers to the various problems arising in their treatment.

Roentgenologically, simple diverticula seldom present difficulties in diagnosis. However, in order to avoid haphazard selection and to facilitate analysis of a sufficiently large number of cases, it is important that the roentgenologist record all diverticula observed, even if they appear to be of no clinical significance.

A critical review of cases previously reported reveals that complications due to diverticula are much less common than generally assumed.^{3,35,36} The usual complication is melena with the diverticulum as the source of hemorrhage.

The treatment of diverticula is primarily conservative and expectant.^{3,26,41} Surgical treatment should not be contemplated until every other possible cause of the symptoms has been eliminated or when complications occur.^{11,20} It has been noted that at operation it may be difficult to find the diverticulum which has been visualized on roentgenograms, probably because the lesion has contracted under anesthesia.^{15,35,42} The surgeon should be aware of this possibility and the preoperative roentgenologic localization of the malformation should, therefore, be precise.

Intraluminal diverticula comprise the smallest number of this group of malformations, and, fortunately, they present no problems of diagnosis or therapy. 8,25 In the reported cases, all but one12 have been in adults. A few cases of intraluminal diverticula were asymptomatic but most of the patients had complaints varying from vague abdominal discomfort to ulcer-like pain. 25,31 There were symptoms suggestive of intermittent obstruction in a few cases. At least 3 patients had melena, although the relationship of the diverticulum to the hemorrhage was confirmed at operation in only 1 of these. 45 Operative treatment is recommended mainly for complications; the results of conservative treatment are generally satisfactory.

Duplications of the stomach and duodenum are rare. The symptoms are related to the site and size of the lesion and to the communication, if any, between the duplication and the functioning part of the gastrointestinal tract. Many duplications are diagnosed at the age of 1 or 2 days due to intermittent vomiting. In several cases, a palpable abdominal tumor and visible peristalsis suggested pyloric stenosis.^{1,38,43} Some investigators have found melena to be a common symptom, particularly in children.4,17,24 In a great percentage of adult cases, the symptoms consisted solely of pain and epigastric fullness, most pronounced after eating.7,13 Signs of obstruction were noted in other cases, due to the fact that a relatively small duplication formed the head of an intussusception.²⁴

Diagnosis is difficult, even though the symptoms usually suggest a lesion in one organ or the other. The roentgenologic findings are quite varied, and differentiation from tumors is often impossible. This is particularly applicable in adults.

The danger of complications in duplications appears to be greater in cases with the lesion located in the stomach; this is because the mucosa in the malformation may be physiologically active with resultant autodigestion, mural necrosis and hemorrhage.^{17,20,29} The risk is particularly great in cases where there is no communication between the stomach or duodenum and the duplication.

Treatment is surgical, 20,23,24,29,39 and the procedure is often technically complicated. Furthermore, the concept of duplication is relatively foreign to many surgeons dealing with adults only; they may thus have considerable difficulty in orientating the lesion at operation. The problems are shared to a certain extent by the pathologists, whose task it is to evaluate the microscopic nature of the lesion. In gastric duplication, in particular, available specimens may show obscure changes due to necrosis or autodigestion.

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ADENOMYOMA OF THE STOMACH*

REPORT OF A CASE

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ADENOMYOMAS of the stomach are exceedingly rare tumors. Their recognition, roentgenographically, as benign tumors is of greatest importance. The roentgenographic appearance of a small filling defect in the distal stomach with intact overlying and neighboring mucosa is so characteristic that confusion with a malignant tumor is unlikely.

Adenomyoma of the stomach was first described in 1903 by Magnus-Alsleben⁶ after 5 cases were found incidentally at necropsy. Since that time, 22 additional cases have been reported 1-5,7-11 (Table 1). Of these, only 3 gave roentgenographic evidence on upper gastrointestinal studies that was suggestive of benign antral tumor. In the most recent report of adenomyoma of the stomach, in 1955, Cimmino² doubted that adenomyoma was a separate entity. He expressed the belief that adenomyoma was part of a spectrum of changes in the gastric wall that included aberrant pancreas, Brunner's glands, and undifferentiated myoepithelial growths.

The present authors describe the typical roentgen appearance of a benign antral tumor and the pathologic findings that establish adenomyoma as the histologic entity.

REPORT OF A CASE

A 43 year old white woman was admitted to the University of California Medical Center, San Francisco, on November 15, 1964 because of pain in the midthoracic region of 7 months' duration. There was no radiation of this persistent, interscapular pain, which was aggravated by motion. No history was obtained of abdominal pain, nausea, vomiting, or melena, or of use of antacid substances. The past his-

tory included a left radical mastectomy in 1962 for carcinoma of the breast, an appendectomy in 1959 for acute appendicitis with perforation, and a lumbar laminectomy in 1957 because of disk disease.

The left breast was absent. A soft, tender mass measuring 3×3 cm. was palpated in the right breast with a small, nontender, right axillary lymph node. Point tenderness was present over the midthoracic vertebrae along with left, paraspinal muscle spasm. The abdomen was soft and free of palpable masses. Slight tenderness to deep palpation was present in the midepigastrium.

The roentgenographic appearance of the thoracic spine was normal. A roentgen examination of the upper gastrointestinal tract demonstrated a filling defect in the gastric antrum surrounding an area that retained barium (Fig. 1, A and B).

On exploratory laparotomy, a nodular mass about 2 cm. in diameter was seen in the prepyloric area of the anterior stomach. A pylorectomy and an end-to-end gastroduodenostomy were done.

The pathologist's report described a $2 \times 1\frac{1}{2}$ $\times 1\frac{1}{2}$ cm. lesion arising in the muscularis of the prepyloric region. It was not connected to the overlying normal appearing gastric mucosa. Grossly, the cut surface of the lesion had a whorled appearance. Its brownish-gray color was similar to that of the adjacent normal muscularis, and tiny cystic spaces were identified throughout the lesion. Microscopically, broad, interdigitating bundles of smooth muscle were present between which were focal collections of ducts (Fig. 2, A, B and C). Some of these ducts were dilated and lined by tall columnar epithelium with regular, basallyoriented nuclei. Surrounding some of the ducts were small glands lined with mucus-secreting cells. No pancreatic acini were identified. The microscopic diagnosis was adenomyoma ventri-

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The findings on upper gastrointestinal roentgenograms before the last surgical procedure had been those of a benign tumor of the antrum. A 1.5 cm. mass in the prepyloric area had been surrounded by normal mucosal pattern. Barium remained trapped at the edge of this mass. Peristalsis in the area was not impaired and the area did not appear rigid at fluoroscopy. The roentgenographic appearance at that time was believed to represent an ulcer

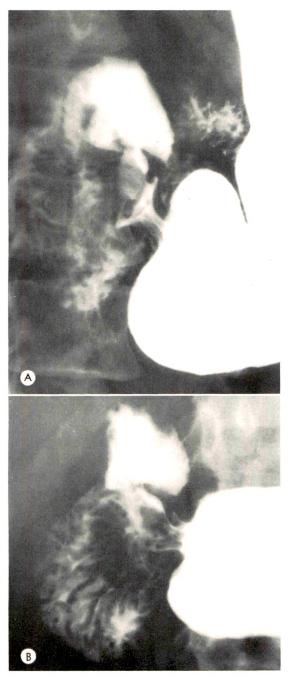


Fig. 1. (A and B) Filling defect in prepyloric region with normal adjacent mucosal pattern. At fluoroscopy, peristalsis was normal in the area.

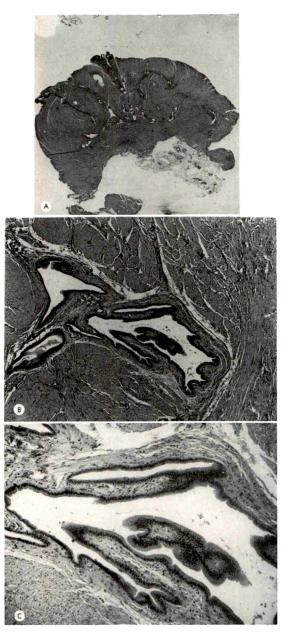


Fig. 2. (A) Low power view of nodular smooth muscle tumor with irregular cystic spaces. (B and C) Cystic spaces in a smooth muscle stroma, lined by tall columnar epithelium.

Table I
REVIEW OF REPORTED CASES

Authors	No. of Cases		Clinical History	Roentgen Findings	Location—Gross Appearance	Histologic Findings
Magnus-Alsleben* 1903	5		Necropsy findings	None	Near pyloric ring	Mixed undifferentiated glandu- lar structures and pancreatic- like acini
Gruzdeff ⁴ 1909	ĭ	36 F	Dyspepsia; palpable right upper quad- rant abdominal mass	None	Posterior stomach wall near pylorus	Epithelial lined cysts in smooth muscle with normal gastric mu- cosa
Eusterman and Senty ⁴ 1922	3	62 M	Peptic ulcer symptoms			Not given, called adenoleso- myoma
		60 F	Past history of gall- bladder disease	None	1×2.5 cm. lesion, greater curvature, anterior wall, 5 cm. from pylorus	Adenoleiomyoma
		28 M	Gastric "neurosis"	None	2 cm. lesion, anterior greater curvature, prepy- loric	Adenoleiomyoma
Moore ⁷ 1924	2		None given	None given	None given	None given
Stewart and Taylor ⁹ 1925	5	46 M	Abdominal pain, occasional vomiting	None	Prepyloric anterior gas- tric wall	Scattered cystic acini of tall columnar epithelium, undiffer- entiated; some pancreatic and Brunner's acini, in smooth mus- cle stroma
		55 F	Epigastric pain	Normal upper gastrointestinal series	Prepyloric anterior stomach wall	Essentially as above with mixed undifferentiated and differentiated epithelial cysts
		49 M	Cerebrovascular accident	None	Prepyloric anterior wall, greater curvature	Mixed in smooth muscle stroma, as above
		50 M	Vague abdominal discomfort	None	Prepyloric, greater curvature	Mixed, as above
		49 M	Vague hunger pains	None	Prepyloric, anterior gastric wall	Mainly cystic acini lined by tall columnar epithelium
Woolsey and Millzner ¹¹ 1928	I	36 F	Vomiting, gnawing epigastric pain	Pylorospasm, no defects noted	o.5 cm. lesion, 2 cm. from pylorus on anterior an- tral wall	Smooth muscle stroma containing undifferentiated epithelial cysts along with Brunner's glands and pancreatic type acini
Rodgers 1934	1	IO F	Projectile vomiting since just after birth		Pyloric tumor	Sharply defined collagenous zone separating ducts lined with cells like those of Brunner's glands from the pyloric muscularis
Clarke 1940	4	18 M	Epigastric pain, nausea, vomiting	Smell, round pre- pyloric defect changing in nature	3 cm. submucosal mass 3.5 cm. from pylorus on anterior antral wall	Interlacing bundles of smooth muscle with cysts lined with low columnar epithelium
		52 F	Epigastric pain with vomiting	None		Smooth muscle stroma with un- differentiated duct-like glands, pancreatic acini and Brunner's glands
		58 F	Severe epigastric pain	Upper gastroin- testinal series un- remarkable	1.5 cm. pyloric submuco- sal tumor with small ul- ceration in overlying mu- cosa	

Table I (Continued)

Authors	No. of Cases		Clinical History	Roentgen Findings	Location—Gross Appearance	Histologic Findings	
	Consideration of the second	39 F	Asymptomatic, found at surgery for ectopic pregnancy	None	Subserosal pyloric nodule	Smooth muscle stroma with cysts and glands of varying de- grees of differentiation, with one pancreatic acinus identified	
Campbell ¹ 1949	3*	37 F	Vague history of indigestion	Normal stomach size and peristal- sis, prepyloric fill- ing defect with in- tact neighboring gastric mucosa	Prepyloric anterior wall lesion with slight depres- sion in otherwise normal overlying gastric mucosa	Mixed gland and duct formation with tall columnar lined spaces and pancreatic-type glands	
Waas, McCloskey and Sullivan ¹⁰ 1951	I	2 F	Hypertrophic py- loric stenosis with surgical repair; pa- tient died of pul- monary emboli	Dilated stomach with narrow elongated pylorus	2 cm. nodular mass on greater curvature side of pylorus	Thickened circular pyloric mus- cle layer containing Brunner's type glands with tall columnar epithelium	
Cimmino ² 1955	I	61 F	Epigastric pain, occasional vomit- ing, slight epigastric tenderness	Round, sharply defined prepyloric lesion with central umbilication and normal surrounding gastric mucosa and peristalsis		Connection of lesion with gastric mucosa, submucosal smooth muscle nodule containing small scattered mucus-secreting glands, no pancreatic acini	
Goldberg and Margulis			2 cm, prepyloric mass on anterior antral wall	Smooth muscle mass in muscu- laris containing duct-like cystic spaces lined by tall columnar epithelium, normal gastric mu- cosa			

^{*} History reported on only 1 of the 3.

DISCUSSION

The histopathologic classification of adenomyomas of the stomach is somewhat controversial. Stewart and Taylor,9 and Clarke³ have suggested the probable origin from epithelial buds incorporated into the wall of the gut in embryonic development. Clarke expressed the belief that these primordial epithelial buds may undergo varying degrees of differentiation, resulting in the eventual histologic spectrum of adenomyoma, hyperplasia of Brunner's gland, and aberrant pancreas. Stewart and Taylor noted that pancreatic-containing adenomyomata and ectopic nodules of differentiated pancreas were comparatively frequent in the prepyloric region. They stated that this occurrence was suggestive of a common etiology of intestinal epithelial rests in the gut wall.

According to Stewart and Taylor's

studies, the essential histologic feature of these tumors is the differentiated and undifferentiated glandular tissue in the submucosa and muscularis of the stomach wall. Often, 3 types of epithelial formation are seen in the same tumor: (1) the most abundant type-undifferentiated epithelium with duct-like channels and large cystic spaces. These are lined by tall columnar epithelium; (2) Brunner's type differentiated epithelium forming glands of subcolumnar and cuboidal cells with small, circular lumina; and (3) pancreatic-typeacini of cuboidal or polygonal cells with practically no lumina. The term "adenomyoma" is justified if evidence of neoplasia is present. Such neoplasia is represented by nodules of glandular tissue. These are surrounded or encapsulated by smooth muscle within either the muscularis or submucosa in a pattern of tumor-like overgrowth. The

adenomyoma differs, then, from heterotopic pancreas in respect to both diversity of glandular structures and neoplastic proliferation.

Clarke attempted to combine adenomyoma and heterotopic pancreas into degrees of the same pathogenetic process: myoepithelial hamartomatous formation. He stated that the term "adenomyoma" should be used only for tumors with smooth muscle and undifferentiated duct-like structures. In those tumors in which all types of differentiation of epithelium are mixed it is not applicable. This latter opinion is contrary to that of Stewart and Taylor. Cimmino proposed one practical classification of adenomyosis. This was to include aberrant pancreas and undifferentiated columnar epithelial glands in smooth muscle stroma, with the histologic distinction left to the pathologist.

The microscopic findings of the present case conform to those in the classification of adenomyoma as described by Stewart and Taylor. Myoepithelial hamartoma, however, would amply describe those tumors with mixed epithelial differentiation. The spectrum of classification of intramural epithelial tumors of the stomach might then well include adenomyoma for the undifferentiated tumors. It would include myoepithelial hamartoma for those of mixed differentiation and aberrant pancreas and Brunner's gland heterotopia for the well differentiated tumors.

No specific age or sex incidence is associated with gastric adenomyomas. Signs and symptoms vary greatly and are not specific for adenomyoma, or even for benign gastric tumors. The symptoms range from vague abdominal discomfort and indigestion to severe midepigastric pain that is indistinguishable from peptic ulcer. Epigastric pain of varying severity was present in 8 patients reported. Vomiting in 7 patients presumably resulted from obstructing prepyloric tumor. In only 1 patient was a lesion in the area of the pylorus clinically palpable. In all of the patients reported, including the present

one, the tumor was in the prepyloric area within 3.5 cm. of the pylorus. Almost all were on the anterior antral wall on the side of greater curvature. They ranged from 1 to 3 cm. in diameter.

ROENTGEN FINDINGS

Of the previously reported cases of adenomyoma, only 9 patients had upper gastrointestinal roentgenograms. In only 3 of this group were findings suggestive of benign antral tumor. Campbell,1 Cimmino,2 and Clarke³ have reported patients whose similar roentgen findings in the gastrointestinal tract were suggestive of a benign gastric tumor. In these patients the stomachs were of normal size. Normal peristalsis, no pylorospasm, and small, round, well defined filling defects of various size in the prepyloric region, with intact surrounding gastric mucosa were present. A central umbilication in the round, sharply outlined filling defect of Cimmino's patient was suggestive of an aberrant pancreas. In the present patient, the roentgen findings were similar to those in patients reported previously. Nothing specific in roentgenograms is indicative of adenomyoma. Indeed, the same findings may point to aberrant pancreas,2 leiomyoma, and other epithelial and mesenchymal benign gastric fumors.

SUMMARY

A case of adenomyoma of the stomach is presented illustrating roentgenographic findings typical of a benign tumor of the gastric antrum. A review of the literature reveals that this rare tumor is located in the anterior wall of the prepyloric region. It is not associated with any specific clinical symptoms, nor with age or sex incidence. The histologic features of this tumor are described, as well as the differing views regarding its pathologic classification.

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FOCAL HYPERTROPHY OF THE PYLORIC MUSCLE— TORUS HYPERPLASIA

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IN ADDITION to the diffuse or generalized hypertrophy of the pyloric muscle that occurs in adults, a focal or localized form also exists. The anatomic basis for this entity derives from the dissections of Torgersen11 who consolidated the previous work of Wernstedt, Cunningham and Cole and correlated it with the phylogenetic background. According to these studies, the pyloric muscle consists of two loops of localized circular muscle fibers. The distal or right canalis loop separates the stomach from the duodenum while the proximal loop obliquely embraces the proximal end of the pyloric canal. On the greater curvature these two loops are 3 to 5 cm. from each other, but on the lesser curvature side the fibers converge to form a muscular prominence called the torus.

In the few reported cases of focal hypertrophy of the pylorus, the hypertrophy seems to correspond anatomically to the torus and thus lends additional validity to the anatomic concept described above. Whether such focal hypertrophy represents an early stage of diffuse hypertrophy or a separate entity is not yet known; although Bachmann,² in 1952, noted it in 12 out of 600 autopsies (2 per cent), he could find only 2 previous similar observations. None of these patients were studied roentgenographically. Since Bachmann's report only 8 additional cases have been described.^{1,5–8,10,12}

Because of the paucity of reported cases, 3 additional patients and I previously reported will be presented and the roentgen findings discussed.

REPORT OF CASES

Case I. I.F. (158-75-49), a 37 year old male, was admitted to the hospital because of heartburn, bloating and eructation of 3 years' duration. Three months earlier he had experienced

a severe attack of right upper quadrant pain. Roentgenograms demonstrated evidence of gallstones and a small hiatus hernia. A deformity was noted on the distal lesser curvature aspect of the gastric antrum, consisting of flattening and widening of the space between the distal antrum and base of the duodenal cap (Fig. 1).

At the time of cholecystectomy, a 2×2 cm. intramural mass was palpated on the lesser curvature of the pyloric channel. A partial gastrectomy was performed and microscopic examination of the nodule disclosed hypertrophied pyloric muscle. On the greater curvature aspect only equivocal muscle hypertrophy was present.

Case II. S.P. (146-66-38) was a 50 year old male who entered the hospital because of a recent episode of melena. A 4 year history of duodenal ulcer had been documented elsewhere by multiple roentgenographic examinations. Roentgenographic examination of the upper gastrointestinal tract at this hospital revealed a deformed duodenal bulb containing a small crater. In addition a small rounded defect was noted on the distal aspect of the lesser curvature of the antrum, pyloric channel and base of

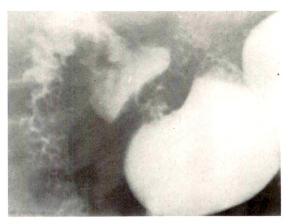


Fig. 1. Case 1. Deformity on distal lesser curvature consisting of flattening and widening of space between base of duodenal bulb and antrum on the lesser curvature side.

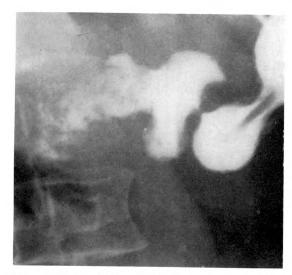


Fig. 2. Case II. Deformity of distal antrum similar to that seen in Case I but less pronounced.

the duodenal bulb on the lesser curvature side (Fig. 2).

A subtotal gastrectomy was performed because of the duodenal ulcer. Palpation of the specimen disclosed a small firm intramural nodule in the pyloric region which proved to be smooth muscle hypertrophy on microscopic examination.

Case III. F.B. (146-40-60), a 65 year old female, was found to have positive guaiac stools during the course of a routine check-up. Roent-genographic examination of the upper gastro-intestinal tract done elsewhere was allegedly negative but she was advised to have it repeated in 3 months. This was done and she was referred to the Columbia-Presbyterian Medical Center for evaluation and treatment. Roent-genographic examination performed here showed a flattening of the distal 2 cm. of the lesser curvature of the antrum which at times exhibited a small niche in the mid portion of

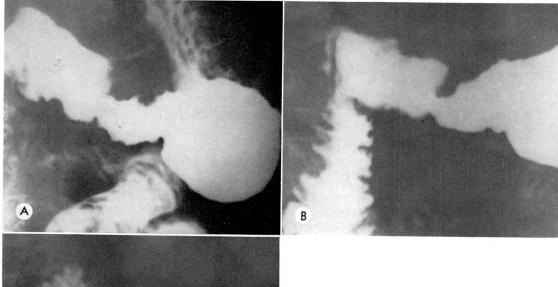




Fig. 3. Case III. (A) Deformity of distal antrum, characterized by flattening, and a small protrusion suggesting a niche. B and C demonstrate the changing contour of the deformity and the transient nature of the niche.

the flattened area (Fig. 3, A, B, and C). A similar appearing lesion was present on the outside roentgenograms made 3 weeks before.

The only symptom which could be elicited was mild substernal and epigastric distress occurring several hours after meals and relieved by antacids. Multiple stool examinations were consistently guaiac positive. The hemoglobin level was 11 gm. per cent. A clinical diagnosis of probable gastric carcinoma was made and a subtotal gastrectomy was carried out. A 1 cm. smooth, firm, round, freely movable nodule could be palpated at the lesser curvature aspect of the pyloric ring. The overlying mucosa was slightly atrophic but intact. Microscopic examination disclosed focal hypertrophy of the smooth muscle and marked atrophic gastritis of the mucosa.

Case IV (previously reported⁹). H.G.S. was a 49 year old white male with a 2 year history of recurrent epigastric and right upper quadrant pain which was not related to food intake nor relieved by antacids. The roentgenograms of the stomach were interpreted as negative. A partial gastrectomy was performed and a 2×2 cm. firm submucosal nodule was found at the lesser curvature side of the pyloric ring which on microscopic examination proved to be focal hypertrophy of the pyloric muscle.

DISCUSSION

In most of the reported cases, the stomach was otherwise negative except for one case with an associated gastric ulcer and 5 patients with gastritis. The predilection for the male sex was not as striking as in concentric hypertrophy since the male-female ratio was 15 to 11. As yet, this type of pyloric hypertrophy has not been observed in children.

A total of 26 cases have been reported in the literature. In 1946 Chene and Spriet,³ in their discussion of pyloric hypertrophy, mentioned a nodular type that always occurs on the lesser curvature, and is always found accidentally. The 12 cases described by Bachmann² in 1952, as well as the 2 others which preceded his report, were incidental autopsy findings and none of the patients had been examined roentgenologically. The 12 cases that have appeared

in the literature since those of Bachmann are summarized in Table 1.

In 6 of the 8 previously reported patients, the distal antrum and pyloric area were thought to be within the limits of normal. The remaining 2 patients were described as having a filling defect on the lesser curvature or flattening of the distal lesser curvature. Of the 4 patients reported above, 1 showed no definite evidence of roentgenographic abnormalities (Case IV) and 2 others exhibited slight flattening of the distal lesser curvature and an increase in the space between the base of the duodenal bulb and distal antrum. This finding was more pronounced during complete distention of the antrum and tended to disappear during a muscular contraction (Fig. 1 and 2). The fourth patient exhibited an unequivocal abnormality consisting of not only flattening of the distal lesser curvature of the antrum but also a small protrusion suggestive of an ulcer niche. It is unlikely that the latter actually represented an ulcer since it was not constant (Fig. 3, A, B and C) and the mucosa was intact at the time of surgery which was only 10 days after the roentgenographic examination. It was later discovered that this patient had been taking 10 aspirin tablets daily which might have accounted for her guaiac positive stools.

The fact that the location of the focal hypertrophy coincides with the site of the torus justifies the name torus hyperplasia. According to Keet,⁶ the fact that a certain portion of the pyloric muscle is able to undergo hypertrophy implies that it has a specialized function or structure. More difficult to explain are the 2 reported cases of focal pyloric muscle hypertrophy localized on the greater curvature side.^{4,7} These have been omitted from this paper because they cannot be properly included under the title of torus hyperplasia.

It is impossible to determine, at the present time, whether such focal hypertrophy represents a separate entity or an early stage of diffuse hypertrophy. Skoryna *et al.*¹⁰ believe that in some in-

TABLE I

	Sex	Age	Symptoms	Duration	Roentgenographic Findings	Therapy	Pathology
I. Mack ^a	F	67	Intermittent nausea	1½ yr.	Filling defect on lesser curvature	Partial gastrectomy	Flattening of distal antrum on lesser curvature side; stomach otherwise negative
2. Wellmann et al. ¹³	М	77	Epigastric pain	6 yr.	? Narrowed antrum	None	Autopsy revealed hypertrophy confined to lesser curvature re- gion of pylorus, 11 mm. thick; stomach otherwise negative
3. Knight ⁷	F	56	Epigastric pain	3 mo.	Mild gastric retention	Local excision	I cm. nodule on anterior superior surface of pylores
4. Knight ⁷	F	46	Right upper quadrant pain	17 mo.	Negative	Local excision	I cm. pyloric nodule; chronic gastritis
5. Heidenblut	M	48			Negative		Gastritis and penetrating ulcer
6. Keet ⁸	M	50	Ulcer symptoms	12 yr.	Lesser curvature ulcer proximal to pylorus	Partial gastrectomy	Pea-sized mass of focal hyper- plasia of circular muscle at lesser curvature aspect of pylorus; benign ulcer
7. Skoryna et al. ¹⁰	F	52	Upper abdominal pain, weight loss, nausea and vomiting		Negative	Partial gastrectomy	Small nodule on lesser curvature side of pyloric canal
8. Albot and Magnier ¹	М	52	Epigastric pain		Flattening of distal lesser curvature	Partial gastrectomy	Smooth muscle hypertrophy and gastritis
9. Seaman*	M	49	Epigastric pain	2 yr.	Negative	Partial gastrectomy	13 mm. oval mass on lesser curv- ature side of pyloric channel
10. Seaman*	M	50	Epigastric pain	4 yr.	Flattening of lesser curvature of pylorus	Partial gastrectomy	Small nodule of hypertrophied smooth muscle
II. Scaman ⁹	М	37	Duodenal ulcer	4 yr.	Duodenal ulcer; deformities of lesser curvature side of pylorus	Partial gastrectomy	2 cm. nodule palpated during surgery
12. Seaman*	F	65	Mild epigastric distress	4 mo.	Flattening of dis- tal lesser curva- ture with 3 niches	Partial gastrectomy	Focal smooth muscle hypertro- phy and atrophic gastritis

stances it may progress to a more extensive form, involving the entire circular musculature of the pyloric canal.

SUMMARY

A rare form of hypertrophy of the pyloric muscles, occurring only in adults, is focal hypertrophy or torus hyperplasia. Four examples are described thus bringing the total reported cases to 27. Five of the 13 patients examined roentgenographically demonstrated a flattening of the distal 1 to 2 cm. of the lesser curvature of the antrum and asymmetric widening of the interval

between the stomach and base of the duodenal bulb.

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GASTRIC ULCERS AFTER 70*

By J. R. AMBERG, M.D.,† and F. F. ZBORALSKE, M.D.,†

THE radiologist's responsibility in the clinical problems of gastric ulceration has been simplified in recent years. The basic tenet is that the initial roentgen diagnosis should be benign gastric ulcer, carcinoma of the stomach, or indeterminate. The latter group should represent only a very small percentage of the cases. If the clinical condition of the patient permits, surgical management is indicated for the neoplastic and indeterminate group, and a trial of medical management for those patients in whom benign gastric ulcer was diagnosed. The discovery of the distinguishing features of benign and malignant gastric ulceration has made this approach possible. Dodd and Nelson⁷ have recently brought this material up to date with great clarity.

In the past, we have accepted this diagnostic-therapeutic regimen and applied it to all patients with the diagnosis of gastric ulcer. It is known that geriatric patients do not tolerate gastric operations as well as does the younger patient. Further, we believed that both the natural course of benign gastric ulcers and their anatomic location differed significantly in the elderly. We deemed it important, therefore, to determine if the usual regimen of gastric ulcer therapy in these patients should be altered. Accordingly, the records and roentgenograms of aged patients who had a roentgenologic diagnosis of benign gastric ulcer were re-evaluated.

MATERIAL

In the 5 year period, 1958 through 1962, 73 patients of 70 or more years had had benign gastric ulcers diagnosed roentgenologically at Milwaukee County General

Hospital. This number included both inpatients and out-patients.

AGE AND SEX

At the time the ulcer was diagnosed, 49 of the patients were in their seventies and 24 in their eighties. There were 39 men and 34 women.

SYMPTOMS

The symptoms in this group were not unusual. Those that led to roentgen examination were mainly abdominal pain, vomiting, and anemia.

ROENTGEN FINDINGS

The locations of the ulcers are shown in Table 1. Of main interest was that the ulcers were frequently high along the lesser curvature (Fig. 1). At this site they were commonly located on the posterior wall, either within the cardia of the stomach or, more frequently, high in the body just distal to the cardia. In 31 of the 73 patients (42 per cent), the ulcer was in this location. Considering all age groups, the incidence of ulcers in this area is considered to be approximately 8 per cent.³

In 16 patients the ulcer on the lesser curvature was in the more conventional

Table I LOCATION OF ULCER

	No. of Patients	Per Cent
High lesser curvature Lesser curvature, body of	31	42
stomach	16	22
Antrum	22	30
Greater curvature	4	6

^{*} Presented at the Sixty-sixth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., September 28-October 1, 1965.

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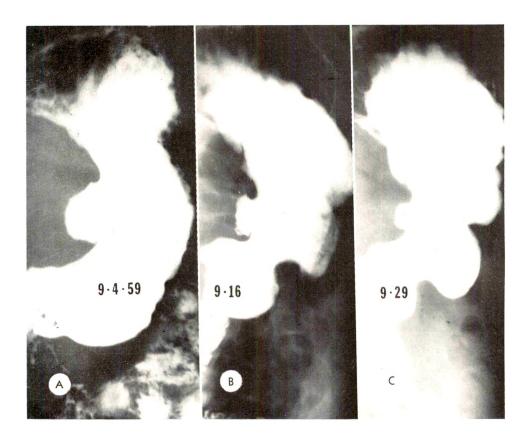


Fig. 1. "Geriatric ulcer."

location, at or just above the incisura angularis. There were 22 ulcers in the antrum. The greater curvature was the site of 4 ulcers.

In the "geriatric ulcer," high along the lesser curvature, healing often leaves the typical "hourglass" deformity (Fig. 2, A, B and C). It was common in the larger ulcers and was also seen when wedge resection of the ulcer had been done (Fig. 3, A, B and C). Obviously, the deformity reflects the magnitude of the original ulcer. This deformity is not commonly seen in younger patients.

Healing was difficult to quantitate since a standard therapeutic regimen and a regular schedule of roentgen re-examination were not followed. Ulcers larger than 2 cm. apparently required a longer time to heal in the older patient. More commonly, a month rather than 2 weeks was necessary before the ulcer was reduced to half size and 2 months were often required for complete



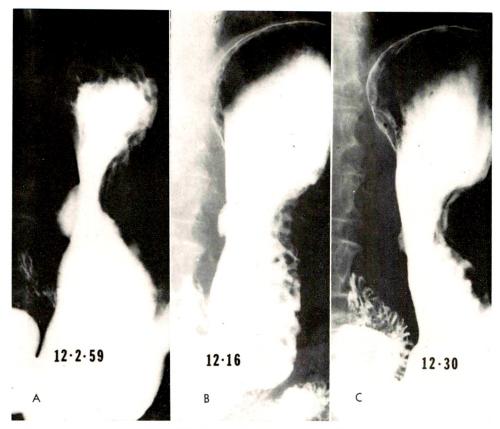


Fig. 3. (A, B and C) Delayed healing. After 4 weeks a good sized crater still remains.

healing (Fig. 4 and 5, A–E). This slower healing confirms previous studies, ¹⁷ which showed a delayed rate of healing in the aged.

TREATMENT

For purposes of discussing treatment and its effectiveness, the patients have been divided into 2 groups: those treated medically only and those having surgical treatment.

MEDICAL GROUP

A total of 44 patients was treated medically, without any surgical intervention. The manner of treatment varied. Some

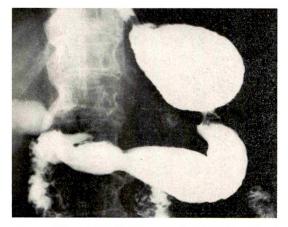


Fig. 4. The "hourglass" stomach which is typical of the healed high lesser curvature ulcer.

Fig. 2. (A, B and C) Healing of these large ulcers in the aged often takes more than 1 month; as the ulcer heals, the appearance of a mass about the crater increases.

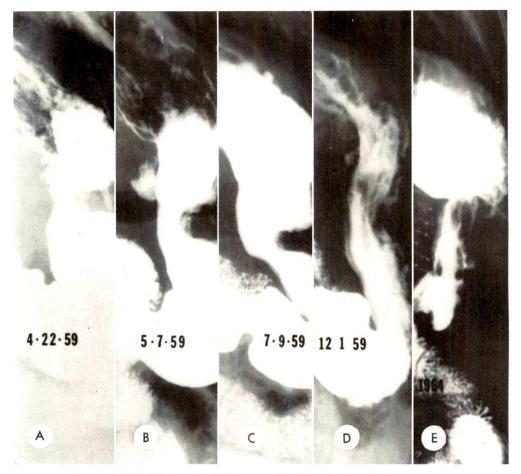


Fig. 5. (A-D) "Geriatric ulcer" marked by slow healing and recurrence.
(E) Five years later, deformity after wedge resection and vagotomy.

were treated entirely as out-patients; others were treated in the hospital until the ulcer had healed.

Only 8 of the 44 persons were still living at the time the follow-up study was completed. The exact cause of death was not known in 13 of the 36 who had died. In particular, information was not available to determine if gastric ulceration contributed to death. The other 23 patients were under observation at the time of their death. Nine of these died of gastric ulceration.

Of the 44 patients, only 14 survived 2 years after their diagnosis of gastric ulcer. This poor rate of survival reflects primarily the presence of other serious illnesses in these patients, such as malignant, cardiovascular, or pulmonary disease. In some

patients the concomitant disease was so severe as to limit management of the ulcer. Often, because of the patient's debilitated state, surgical procedures could not be considered.

SURGICAL GROUP

The 29 patients in the surgical group underwent a total of 30 operations. In 7 instances, bleeding or perforation forced emergency operations, with subsequent deaths of 2 patients (29 per cent). In the group of patients in whom 23 elective operations were performed, 3 died (13 per cent). In 6 patients the elective procedure was done because of recurrence after previously successful medical management.

A total of 19 of the 24 patients who sur-

vived the operation were alive at the end of 2 years (79 per cent). None of these patients suffered recurrent gastric ulceration. The composition of the medical and surgical groups differs so greatly that a comparison of the two in an attempt to establish the best mode of therapy is of no value.

DIAGNOSTIC ERRORS

Three of the patients did not have benign gastric ulcers. One patient operated on because of a presumed benign recurrent antral ulcer had an ulcerating superficial carcinoma of the stomach. This patient was alive and well, without evidence of recurrence, at 2 years. Another patient had an ulcerating leiomyoma. In a third patient, no gastric ulceration was observed at surgical exploration but a severe deformity of the greater curvature was present. This deformity was secondary to dense perigastric adhesions but its etiology could not be determined. It may have been the result of previous perisplenic hemorrhage, pancreatitis, or perforated gastric ulcer.

DISCUSSION ETIOLOGY

The acid-pepsin theory as the cause of gastric ulcers is certainly acceptable for a large number of ulcers observed in this series. This theory is particularly applicable to 8 patients who had associated duodenal ulcers. In these patients the gastric ulcer was either in the antral area or in the middle third of the stomach near the incisura angularis. None was situated in the high lesser curvature.

The possibility of a different cause or another factor contributing to the "geriatric" ulcer is intriguing. In recent years, the concept that all gastric ulcers are acid-pepsin produced has been again challenged. Two patients with gastric ulceration and apparent achlorhydria have been reported recently. Life Elkeles has suggested that gastric ulcers in the aged may be caused by an impaired blood supply. He expressed the belief that the high incidence of calcific plaques in the major vessels leading to the

stomach may be extremely significant, especially when associated with ulcers high on the lesser curvature. The concept that vascular insufficiency may induce gastric ulcers is not new; it has gained few advocates, however, because supportive experimental evidence was lacking.¹¹

With the sophisticated angiographic techniques now available, meticulous study of the blood supply of the stomach in patients with gastric ulcer would appear worthy of investigation.

MEDICAL MANAGEMENT

Regardless of the cause of gastric ulcer, medical management effects healing remarkably. Diserens, Beman, and De Lor,6 in reporting on medical management and follow-up of 236 patients of all ages, recorded only 8 deaths either primarily or secondarily attributable to the gastric ulcer. Often disregarded in reports of this kind is the recurrence rate. Larson, Cain, and Bartholomew¹² followed 391 patients of all ages with gastric ulcers, for 10 to 19 years after initial diagnosis. The ulcer recurred in 73 per cent of these patients and in two-thirds of the patients the ulcer symptoms persisted.

SURGICAL MANAGEMENT

Gastric resection or local ulcer resection, plus measures to reduce acid are also extremely effective. Recurrence after operation is a rarity, an important factor as gastric hemorrhage is poorly tolerated by the aged patient.^{4,14}

Unfortunately, the aged also tolerate gastric operation poorly. The 23 elective surgical procedures in our patients constitute only a small number for evaluation. Nevertheless, the 3 operative deaths produce a mortality rate that cannot be taken lightly. Recent reports of large series of patients of all ages give operative mortality rates from 2 to 5 per cent. Better mortality rates in the aged may perhaps be anticipated with improved preoperative preparation and patient selection.^{2,4,5,9,12,18}

During the same period, 1958 to 1962,

17 patients more than 70 years of age underwent surgical procedures for gastric cancer which had been diagnosed roent-genologically at Milwaukee County General Hospital. In 2, however, the lesions proved to be benign gastric ulcers, both resulting in operative death. These were large ulcers with extensive edema which simulated a mass. As with the giant duodenal ulcer, the large acute gastric ulcer resembling gastric cancer is often a formidable surgical problem. The mortality associated with a false positive diagnosis of gastric cancer has not been properly emphasized.

THREAT OF MALIGNANCY

In only 1 of the 73 ulcers thought to be benign was a malignant lesion discovered and this proved to be a superficial carcinoma. This lesion offers an excellent prognosis as has been recently re-emphasized by Mason.¹³ It is encouraging that the criteria for establishing benign lesions is still effective in this age group in which a significant amount of cancer occurs.

ROENTGENOLOGIST'S ROLE

The detection of the "geriatric ulcer" may at times be difficult. Special attention given to the high posterior wall of the stomach in the aged patient has been helpful to us. A roentgenogram obtained with the patient in the erect position, either lateral or oblique, may aid in detection of an ulcer in this site.

Delayed healing is another characteristic of the "geriatric ulcer." One fact must be accepted; the same substantial healing that occurs in 2 to 3 weeks in the younger patient may not take place in the aged. A slow rate of healing should not suggest a malignant process nor any other threatening situation.

Awareness of the operative mortality would suggest that medical management be initiated after the roentgen diagnosis of gastric ulcer. Especially is this true in those gastric ulcers considered at first roentgenologic examination to be of indeterminate nature, or possibly malignant.

Primary medical management offers

many benefits: (a) it permits improvement of nutrition; (b) the commonly accompanying anemia may be gradually corrected without toppling the precarious homeostasis of the other organ systems; (c) if later surgical treatment is decided upon, whether for benign or malignant disease, the patient may have become a better operative risk; (d) if the ulcer is benign, even a penetrating one, considerable improvement in inflammatory changes will have occurred; and (e) when the resection is done after the resolution of the edema and partial healing of the ulcer, the surgeon then is aware that he is approaching a benign lesion. This initial approach might prevent premature and disaster-prone surgical attacks on benign gastric ulcers.

The typical "geriatric ulcer" is prone to recurrence. Its successful healing and a decision to continue medical management demand periodic roentgen examinations. Extremely large ulcers may develop with only minimal symptoms, often ignored by the patient. The early detection of recurrence may allow surgical excision at a time when the patient is a much better operative risk.

CONCLUSIONS

The clinical material was reviewed of 73 patients with gastric ulcerations originally diagnosed as benign by roentgen examination. The characteristic "geriatric ulcer" was high along the lesser curvature in 42 per cent of these patients. Delayed healing and deformities after healing were characteristic of these ulcers. The roentgen diagnosis was usually accurate, indicating the value of the established criteria that define benign and malignant ulceration.

A conservative attitude regarding immediate elective surgical procedures in the aged is proposed. A preliminary period of medical management is suggested for all patients with ulcerating gastric lesions in this age group.

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DIFFUSE GASTRIC ABNORMALITY—BENIGN OR MALIGNANT?*

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THE differential diagnosis of or abnormal appearing gastric rugae is THE differential diagnosis of enlarged a problem with which the radiologist is occasionally confronted. He may find it exceedingly difficult to categorize the alteration as benign or malignant. In such cases he may be forced to content himself with listing a number of diagnostic possibilities, including lymphoma, carcinoma, gastritis, and mucosal hypertrophy.

For this study, there was collected a group of cases which presented a diffuse abnormality of mucosal contour and fold pattern but without obvious areas of localized tumor or ulceration to simplify the differential problem. A number of features tended to support the diagnosis of a benign gastropathy, whereas certain other findings favored malignant disease. These findings are presented as an aid to the radiologist in the assessment of diffuse gastric abnormality.

MATERIAL

One hundred and seventy-six cases of benign and malignant gastric disease from the files of the Massachusetts General Hospital were reviewed; 155 were obtained from the surgical-pathologic and autopsy files for the years 1954-1963 inclusive, and 21 from the radiology teaching files for the vears 1936-1963. There were 59 cases of gastritis, 85 of carcinoma, 23 of lymphoma, 3 of polyposis, 2 of mucosal hypertrophy, I normal variant, I neurofibrosarcoma, and leimvosarcomas. Some cases lacked pathologic confirmation and were discarded. Also eliminated from further consideration were many cases for which roentgen films obtained prior to 1958 had been destroyed.

Forty-seven of the cases were diagnosed

histologically as acute or chronic gastritis, almost invariably in association with gastric or duodenal peptic ulcer disease, and these cases were excluded as there was no roentgenologic evidence of diffuse gastric abnormality.

All but 13 of the malignant cases were discarded because they showed evidence of intraluminal masses, rigidity, extrinsic gastric tumor, or other features commonly indicative of malignant change.

The cases of polyposis presented as either isolated scattered polypi or as a cluster of enlarged folds with a polypoid appearance. None of these cases showed roentgenologic or pathologic evidence of malignancy. As it is widely recognized, however, that polyps may undergo malignant change without roentgenologic or endoscopic evidence, it was decided to exclude polyposis from further study.

Twenty-nine cases in total were retained for detailed study, as they were diagnostic problems and were illustrative of roentgen features pertinent to this study. There were 16 benign cases including 12 of chronic gastritis, 2 of mucosal hypertrophy, I normal variant and I diffuse edema associated with subdiaphragmatic abscess. There were 13 malignant cases including 4 of carcinoma and 9 of lymphoma.

ROENTGENOLOGIC FINDINGS

On review of these cases, more than a dozen relatively distinct roentgenologic manifestations were noted. Each case was then analyzed as to the presence or absence, and in some cases the degree of prominence, of each sign. Some of these manifestations were present in most of the cases, whether benign or malignant; others

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were observed in only a few. The signs which were noted most often and those which are believed to provide a basis for making a differential diagnosis will be described below, with a tentative evaluation of each.

ANGULAR CONTOUR

The designation "angular contour" has been applied to a gastric outline which consists of more or less straight segments a few millimeters to I or 2 cm. in length, intersecting at obtuse angles, producing the appearance of a series of low mesa-like or broad angular projections (Fig. 1, 2 and 3). When this appearance is noted over a distance of several centimeters, particularly along the greater curvature aspect of the body of the stomach, it appears to favor strongly the diagnosis of a malignant process. One or two angular contours, however, over a distance of a centimeter or two are not considered significant. This sign was present in 4 of 9 cases of lymphoma and 2 of 4 cases of carcinoma; it was not noted to a significant degree in any of the benign cases.

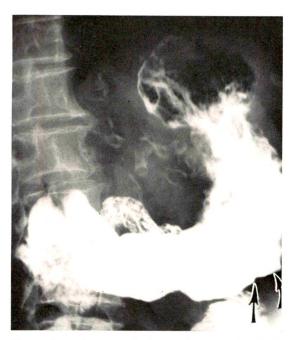


Fig. 1. Lymphoma (reticulum-cell sarcoma). Angular contours along greater curvature of lower body (arrows).

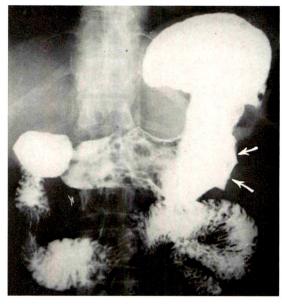


Fig. 2. Lymphoblastic lymphoma. Angular contours along greater curvature of body (arrows).

SCALLOPED CONTOUR

The so-called scalloped contour appears to be related to the angular contour just described and is usually seen in association with the latter, in which event either may predominate. This appearance is also best appreciated on the greater curvature along



Fig. 3. Lymphoma. The greater curvature of the body and antrum shows a succession of angular and scalloped contours.

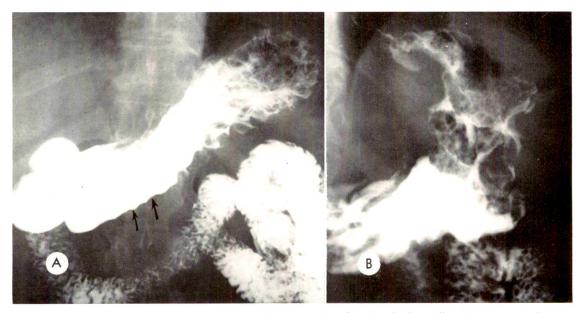


Fig. 4. Adenocarcinoma of stomach. (A) Original examination showing finely scalloped contour and questionable angularity along lower greater curvature (arrows) and nonspecific thickening of rugae along midgreater curvature. (B) Same patient 3 years later, with extensive tumor involvement of fundus and body.

the lower body and proximal antrum. It is produced by a succession of low rounded projections into the gastric lumen measuring several millimeters in length along the base and only 2 or 3 mm. in height. At the junction of 2 such filling defects, a small obtuse point projecting outward from the lumen is formed. A succession of such defects forms a scalloped contour (Fig. 3, and 4A). This configuration should not be confused with an undulating, sine wave-like contour. The filling defects are quite low and unlike the polypoid appearance along the greater curvature of the body sometimes seen in normal patients as well as in the cases here described.

In the 3 malignant cases in which scalloping was seen, angularity of contour alternated with scalloping. Minimal scalloping was noted in 2 benign cases, but in atypical location along the lesser curvature of the body in one and the superior aspect of the fundus in the other.

"PSEUDODIVERTICULAR" APPEARANCE

"Pseudodiverticular," though a quite inappropriate term pathologically, is an apt description of the roentgenologic appearance of a contour, seen usually along the greater curvature of the body of the stomach and lower fundus, produced by a varying number of barium-filled pockets projecting outward from the curvature (Fig. 5, and 6A). When best developed, these pockets are rounded, well filled with barium, and separated by relatively thin septa, resembling the contour due to closely



Fig. 5. Chronic gastritis. Diverticulum-like outpouchings along the greater curvature, separated by thin septa.

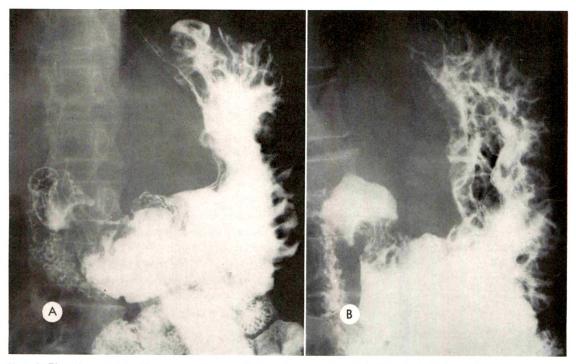


Fig. 6. Chronic gastritis. Numerous deep crevices and several "pseudodiverticula" along the greater curvature. Prominent rugae along the lesser curvature. (A) The crevices along the greater curvature of the lower body of the stomach are distended into angular pockets, separated by thick rugae. (B) With less barium in the body, the "pseudodiverticula" empty and present as deep crevices.

spaced colonic diverticula. Actually, these projections represent the crevices between horizontally oriented folds along the greater curvature. The diverticular appearance is produced when the crevices widen as the stomach is distended with barium, thus separating the folds. When the distention is relieved by passage of barium out of the stomach or by a change in position, the folds again become approximated, and the crevices appear roentgenographically as thin streaks of barium more or less perpendicular to the greater curvature. Thus the pseudodiverticular appearance indicates that the gastric layers deep to the rugae possess some elasticity, militating against the possibility of infiltrating tumor. The distended crevices may also take the form of less well filled projections shaped like a lance tip or even triangles with the base on the greater curvature and the point toward the lumen. When the distended crevices are not tangential to the

roentgen-ray beam, they are naturally less well defined.

Analysis of our cases supports the above observations. The pseudodiverticular appearance was noted in 1 of 9 cases of lymphoma, in 2 of 4 cases of carcinoma, and in 11 of 16 cases of benign disease. Well developed, smooth, rounded "pseudodiverticula" were seen only in benign cases. The presence of this indication of a distensible gastric wall in one area does not, of course, exclude the presence of a malignant process elsewhere in the stomach. In 1 of our cases retrospective evidence of progression of malignant disease was provided by localized obliteration of previously noted "pseudodiverticula."

CREVICES PERPENDICULAR TO GREATER CURVATURE

Crevices running perpendicular to the greater curvature of the body and fundus are frequently seen under normal conditions. With increased height of the gastric

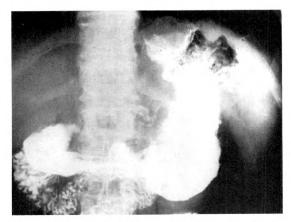


Fig. 7. Lymphoma (reticulum-cell sarcoma). Prominent mound-like filling defects in the fundus. Ragged contour along lesser and greater curvature aspects of body. (This was the only lymphoma that showed more than minimal raggedness of the lesser curvature.)

folds, these crevices show a corresponding increase in depth in both normal and abnormal stomachs (Fig. 6B). Unusually extensive and deep crevices along the greater curvature were noted predominantly in the benign group, with 12 of 16 cases showing mild to marked prominence of crevices. They were present to a mild degree in 3 of 9 cases of lymphoma and in 1 of 4 cases of carcinoma. In only 1 malignant case, a carcinoma, were the crevices very deep and extensive.

MOUND-LIKE FILLING DEFECTS

Low rounded humps, producing moundlike filling defects somewhat larger than those causing the scalloped appearance previously discussed, may be noted anywhere in the stomach, but are most often seen in the fundus (Fig. 7). They tend to be about 1.5 to 3 cm. in length along their base and somewhat less than half as high. They were only questionably more common in the malignant cases, but when they are very marked, the diagnosis of lymphoma is favored. Such an appearance was striking and extensive, however, in one of the benign cases—a severe edema of the stomach secondary to an adjacent abscess in the lesser omental sac.

SMALL WEDGE-LIKE PROJECTIONS

Tiny sharp projections a few millimeters long and usually narrower at the base than they are high, when they occurred, were almost always to be seen along or near the lesser curvature (Fig. 8). They were noted in only 1 of the 13 malignant cases, but in 4 of 16 benign ones. Presumably, they usually represent small ulcerations.

RAGGED LESSER CURVATURE

A number of cases showed, instead of the normal smooth, sharply defined lesser curvature, an undulating or ragged lesser curvature; in some instances the irregularity included the wedge-like projections previously described (Fig. 8). This feature does not appear very helpful in differentiating benign from malignant disease. It

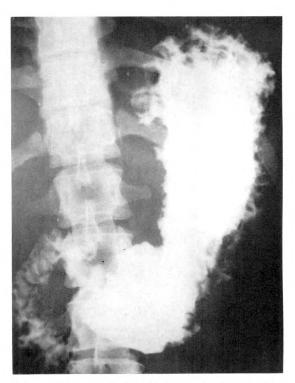


Fig. 8. Acute and chronic hemorrhagic gastritis. Moderate accentuation of depth and number of clefts along greater curvature. Lesser curvature of body very ragged, with a few tiny sharp wedge-like projections. One mesa-like angular projection along greater curvature aspect of proximal antrum; this minimal degree of angularity is not of value in differential diagnosis.

was noted in 3 of 9 lymphomas, 3 of 4 carcinomas, and 8 of 16 cases of benign disease.

PROMINENT LESSER CURVATURE FOLDS

The lesser curvature of the body of the stomach normally is smooth, and for a distance of a centimeter or more lateral to it there is little evidence of longitudinal folds. In this series 7 of the 16 benign cases showed a conspicuous longitudinal fold or two paralleling the lesser curvature (Fig. 6A). These were particularly prominent in the 2 examples of mucosal hypertrophy (Menetrier's disease). A moderately prominent lesser curvature fold was noted in 2 of 9 patients with lymphoma, but in none of the carcinoma group.

SERPENTINE FOLDS

Rugae having a contour approximating the letter "S" in degree of tortuosity were designated "serpentine folds." In 1 case an apparent mass along the greater curvature of the body was shown by compression spot roentgenograms to consist chiefly of such a fold. These folds (usually only 1 or 2) were seen in 5 of the 16 benign cases and in none of the malignant cases.

THICKNESS OF STOMACH WALL

Quite frequently, it is possible by careful inspection to outline a portion of the outer wall of the stomach, sometimes over a distance of several centimeters, thus permitting a measurement of the wall thickness. This thickness, however, both in the normal and the abnormal stomach, will vary markedly, depending upon the portion of the stomach involved and, more significantly, the degree of distention. We have occasionally noted on plain roentgenograms an essentially empty stomach showing an apparent wall thickness of about 1.5 cm., diminishing to 3.0 or 4.0 mm. following moderate barium filling. Also, in the abnormal stomach the outer wall may not be visible in the area of concern.

In this series this was not a very fruitful observation. In 13 benign cases where a

measurement could be made, the range in the barium-filled stomach was 3 to 8 mm., with an average of 5 mm. Of 10 malignant cases, the range in 9 was from 4 to 11 mm., with an average of 8 mm.; in the other case the thickness ranged up to 20 mm. or more. In instances where crevices or "pseudodiverticula" were present, this measurement was made from the bottom of the crevices; thus, in these instances the height of the rugae was not included in the measured thickness. The figures perhaps provide support for tentatively proposing that in these instances of diffuse gastric abnormality, a wall thickness in a moderately distended stomach of 1.0 cm. or over is suggestive of malignancy, particularly when the measurement can be made from the bottoms of interfold crevices. Unusual granulomatous processes can, however, produce a thick stomach wall.14

DISCUSSION

The differential diagnosis of diffuse gastropathies is difficult clinically as well as roentgenologically. Symptomatology may be much the same in benign and malignant processes. Long duration and periodicity of symptoms favor benign disease, but neoplasm may be superimposed upon a benign process without significant change in symptoms. Matzner et al.13 and Texter et al.17 have each reported a case of submucosal gastric carcinoma complicating long-standing benign disease, with gastroscopic and roentgenologic evidence of benign giant rugae over a period of 10 and 14 years, respectively. Each of these reports is illustrated by a single roentgenogram of the stomach obtained following the onset of malignant change. By our criteria, the roentgenograms were suggestive of carcinoma. Twelve cases of carcinoma of the stomach in association with hypertrophic gastropathy have been reported.4

Laboratory determinations rarely clarify the problem. Anemia may occur in association with either a benign or malignant process and may be caused by unrelated coincident disease. On an arbitrary acceptance of a hemoglobin of 11 gm. or less as indicative of anemia, 3 patients with benign disease and 5 with malignant disease in this series were anemic. Usually, a more marked anemia is seen in the malignant case.7 Free hydrochloric acid may be absent in either benign or malignant disease. In 3 of our benign cases, there was no detectable acid after histamine stimulation. Vaughn et al.18 reported absence of free hydrochloric acid in 12 of 41 cases of chronic gastritis. According to Bockus,² 75 per cent of patients with gastric carcinoma show either achlorhydria or marked hypochlorhydria by ordinary fractional gastric analysis, leaving only 25 per cent showing values in the normal to elevated range.

Endoscopy with biopsy is frequently diagnostic. The lesion may, however, be inaccessible to the gastroscope, or the biopsy specimen may be taken from an area without characteristic change. Submucosal cancer may co-exist with benign mucosal disease and escape detection. In this study, endoscopic findings with histologic diagnoses were available in 12 cases. The endoscopist correctly determined that the lesion was benign or malignant in 8 cases; an incorrect interpretation was made in 2 cases, and in 2 the findings were not considered diagnostic.

The roentgenographic demonstration of enlarged gastric rugae usually signifies disease. Occasionally, however, such a stomach will be normal by endoscopy and histology. Many factors have been implicated in the causation of enlarged but otherwise normal folds, including allergy, dietary indiscretions, and toxins.⁷

Enlarged benign fold patterns may occur following surgical trauma to the stomach¹⁹ or as the result of a contiguous inflammatory process, such as a subdiaphragmatic abscess.

In this study we have not attempted to differentiate between individual entities in the benign and malignant groups, but rather to find features that will help to place the patient in one or the other group. We would emphasize that a diagnosis should not be made on the basis of any one sign, but rather, as in the evaluation of a gastric ulcer, by searching for and weighing as many individual roentgenologic manifestations as possible.

Angularity of the stomach contour extending over a distance of several centimeters, sometimes combined with a finely scalloped contour, even when this appearance was variable and not necessarily associated with loss of pliability, appeared to be relatively specific for malignant disease. This appearance was best appreciated along the greater curvature of the proximal antrum and distal body of the stomach.

Unusually deep interfold clefts roughly perpendicular to the greater curvature of fundus and body suggest a benign process. This is particularly true when the clefts are fairly uniformly spaced and are distributed over a distance of several centimeters. If, however, a subsequent examination shows localized obliteration of such clefts (as distinguished from nonfilling because of inadequate distention), malignancy should be suspected.

When distensibility of the gastric layers deep to the rugae is demonstrated by a "pseudodiverticular" appearance along the greater curvature, malignant disease in the area is unlikely. It is especially reassuring when the "pseudodiverticula" are well defined, rather numerous, and separated by thin partition-like folds.

Small sharp projections from the lumen, best recognized along the lesser curvature and probably representing crack-like mucosal ulcers, are probably more common in benign disease. Thick longitudinal folds along the lesser curvature of the body, particularly when they are very conspicuous, also favor benign disease.

Low mound-like filling defects occur in benign and malignant disease. Such an appearance in the fundus, if very prominent, is suggestive of lymphoma.

When an abnormal area can be shown to consist of markedly tortuous, S-shaped folds, benign disease is suggested.

Thickness of the gastric wall, even when

it can be measured accurately, will probably not be helpful in most cases. We would tentatively submit that a thickness of 1.0 cm. or over favors malignancy, particularly when it can be measured from the bottom of interfold crevices in the distended stomach.

SUMMARY

A group of cases showing diffuse alteration in contour and fold pattern of the stomach has been analyzed in terms of roentgenographic manifestations which favor benign or malignant disease. Angularity of contour and a wall thickness of 1.0 cm. or over favor malignant disease. Features more common in the benign cases include deep and distensible crevices between thick horizontal folds along the greater curvature of the body, prominent vertical folds along the lesser curvature, localized S-shaped folds and crack-like projections from the lesser curvature. It is felt that search for and evaluation of the several criteria discussed will aid in differentiating benign from malignant diffuse gastropathy.

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THE POSTPYLOROPLASTY ANTRUM*

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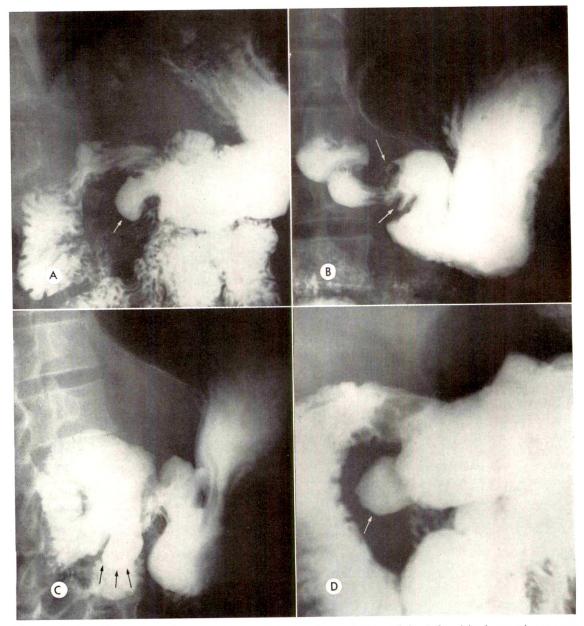


Fig. 1. Roentgenograms of 4 different patients demonstrating variations of the deformities in gastric contour that have been encountered. These patients were all asymptomatic at the time of examination. (A) A well-defined, pouch-like deformity which was visualized on all roentgenograms of this patient's upper gastro-intestinal series. (B) Marked deformity of the gastric antrum which was pliable at fluoroscopy and has remained unchanged on follow-up examinations. The patient has remained asymptomatic. (C) Marked deformity in a completely asymptomatic patient. There is irregularity of the stomach contour and an associated inferior protrusion. (D) A characteristic pouch-like protrusion along the inferior border of the gastric antrum. Note the similarity to A.

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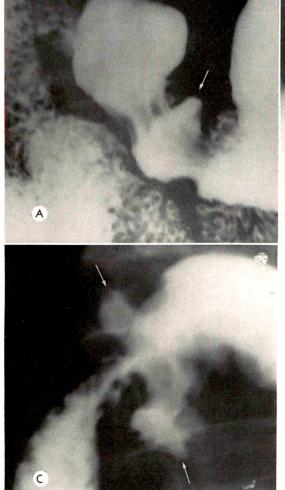




Fig. 2. Roentgenograms made with compression at the time of fluoroscopy. (A) This patient demonstrates projection of barium above the gastric contour. (B) The deformity projects below the gastric contour. This appearance is the one most often encountered. (C) A combination of protrusion above and below the gastric contours. Note the demonstration of normal gastric mucosal pattern in the base of the inferior pouch.

THE surgical approach to peptic gastric ulcer and duodenal ulcer has undergone careful and critical analysis in the past two decades.⁵ As a result, at some centers gastric resection and gastrojejunostomy are giving way to the more conservative pyloroplasty and "total" vagotomy.^{3,6} The normal appearance of the stomach following such a procedure is especially important to the roentgenologist who may be called upon to examine the patient postoperatively.¹

It is the purpose of this report to describe what we consider a characteristic antralpyloric deformity. This deformity should not be confused with an active gastric antral ulcer.

ROENTGEN FINDINGS

All 12 of our patients who were re-examined from 6 weeks to 6 years following vagotomy and pyloroplasty showed this characteristic appearance (Fig. 1, A–D). The fluoroscopist indicated no tenderness associated with the deformity, but, in the first cases examined, the presence of gastric ulcer was suspected. The pouch-like deformity projected from either the inferior, superior, or both gastric borders (Fig. 2, A, B and C). No rigidity was observed. A

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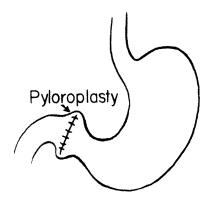


Fig. 3. Line drawing showing the anatomic changes associated with the Heineke-Mikulicz type of pyloroplasty.

normal gastric mucosal pattern was present in each deformity if views were obtained with the pouch only partially filled with barium meal.

DISCUSSION

Reducing gastric secretion of hydrochloric acid by vagotomy and facilitating gastric emptying by pyloroplasty has been advocated by Stempien *et al.*⁴ Although vagotomy alone reduces gastric secretion, it may predispose to gastric ulceration due to delayed emptying.² The transverse closure of the Heineke-Mikulicz type of pyloroplasty apparently creates the characteristic anatomic variation encountered on roentgenograms of the postpyloroplasty stomach.

In their series of 103 patients, Stempien et al.⁴ adjudged 85 per cent to be "entirely satisfactory clinically" on 5 year follow-up. Interpreting postoperative gastrointestinal studies, they described marked pyloroduo-

denal deformity, normal gastric tone and peristalsis, normal gastric emptying time, and normal small bowel transit time.

Figure 3 shows schematically the anatomic deformity associated with the pyloroplasty which resembles the features observed at fluoroscopy and recorded on the upper gastrointestinal series.

SUMMARY

A characteristic antral deformity following vagotomy and pyloroplasty in adult patients is described. It is possible to distinguish this entity from active gastric ulcer even in the absence of an adequate or an accurate history.

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ESOPHAGEAL INTRAMURAL DIVERTICULOSIS*

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IN 1960 Mendl, McKay and Tanners reported what then appeared to be the first recorded patient with "intramural diverticulosis of the esophagus." The purpose of this communication is to record findings in a second patient with the same condition.

The patient reported by Mendl, McKay and Tanner was a 56 year old man who complained of food sticking behind the sternum on swallowing large pieces of solid food. His distress, about 8 months in duration, was usually relieved immediately upon bending forward.

Barium swallow study showed innumerable pinhead sized contrast shadows along the whole length of the esophagus from the level of the second thoracic vertebra downwards, parallel to and 2 mm. outside its smoothly outlined lumen. Most of these showed narrow ducts connecting with the lumen. These appearances were analogous to the roentgenologic image of Rokitansky-Aschoff sinuses in the gallbladder and were believed to represent intramural narrownecked diverticula, i.e., hernial outpouchings of the mucosa through meshes of the muscular layer into the tunica adventitia. The cystic dilatations of the blind ends suggested that they were pulsion diverticula due to increased intraluminal pressure. During fluoroscopy, irregular contractions occurred repeatedly in the lower half of the esophagus assuming, occasionally, a tonic character. The esophagoscope passed easily as far as the cardiac orifice. There was no bleeding and no ulcers were noted. The mucous membrane appeared to be normal.

REPORT OF A CASE

Our case with intramural esophageal diverticulosis was a 52 year old man seen by us at the

Hospital of the University of Pennsylvania in February, 1958. At that time he complained of food blocking his esophagus. This was not a new complaint; apparently 5 times during the previous 5 years he had suffered similar episodes always spontaneously relieved.

The patient had no other significant complaints or clinical findings.

Fluoroscopically, the esophagus revealed moderate increased tone with hyperperistalsis which at times was deep and segmenting (February 3, 1958). Whereas the swallowed OO barium capsule lodged temporarily at the aortic arch, once beyond the aorta it dropped rapidly into the stomach. Of considerable interest was the cervical esophagus above the lodged OO capsule; it was funnel-shaped and revealed marked segmental hyperperistalsis. The latter was seen only when the esophagus was plugged by the OO capsule. With release of the esophageal obstruction, the liquid barium descended rapidly into the hypertonic thoracic esophagus and emptied into the stomach

Roentgenograms of the esophagus revealed numerous intramural esophageal diverticula which mimicked exactly Rokitansky-Aschoff sinuses (Fig. 1, A and B). They had the appearance of the intramural esophageal diverticula described by Mendl, McKay and Tanner.

The diverticula varied in depth from a fraction of a millimeter to several millimeters. They were usually more deep than wide. The tips of some were sharp; others were blunted; occasionally, they seemed to branch in root-like fashion.

Many diverticula lay in halo-like arrangement parallel to the long axis of the esophagus, seemingly not connected to the main esophageal stream—a situation more apparent than real. The diverticula occupied principally the proximal half of the thoracic esophagus with a few demonstrated in the lower half. The patient reported by Mendl, McKay and Tanner exhibited diverticula equally distributed along the entire length of the esophagus, although they were more numerous in the proximal half.

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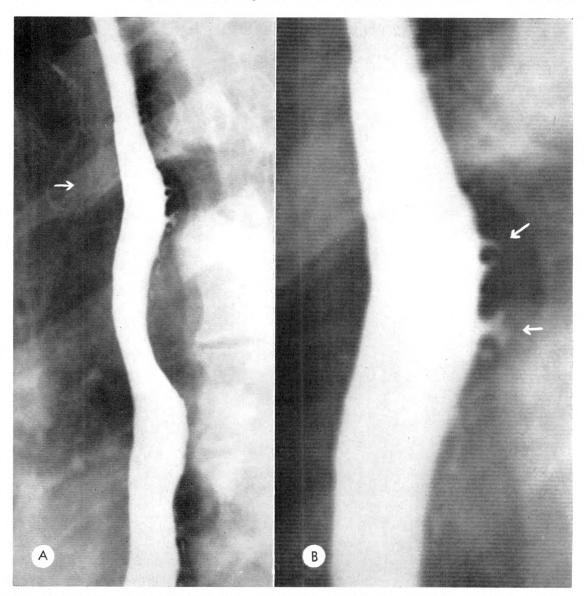


Fig. 1. (A) Barium filled esophagus reveals numerous intramural diverticula. (B) Magnified view of same.

Esophagoscopy performed on February 2, 1958, the day before the above roentgen examination, revealed a large lima bean lodged in the esophagus just above the thoracic inlet. It was removed; no other abnormalities were noted in the esophagus. The mucous membrane appeared normal.

The patient was subsequently re-examined roentgenographically on April 8, 1958, April 15, 1958 and again 3 years later on May 20, 1961. The intramural diverticula were repeatedly demonstrated unchanged. The patient had no clinical complaints.

DISCUSSION

Mendl, McKay and Tanner attributed the esophageal diverticula to a structural abnormality of the esophageal muscular coat. They considered the normally existing gaps in the muscular layer (for the passage of blood vessels, nerves, etc.) to be larger than normal in their patient, thus permitting diverticula to form. They thought, too, that chronic periesophagitis with its subsequent fibrosis may have been related to the process.

The fact that our patient's entire esophagus was hypertonic merits re-emphasis as one recalls that intramural gallbladder diverticula (Rokitansky-Aschoff sinuses) are best demonstrated in the contracted gallbladder.

Whereas one cannot gainsay the validity of Mendl, McKay and Tanner's theory concerning the formation of intramural esophageal diverticula, bearing in mind the common occurrence of dilated bronchial glands seen bronchographically in chronic bronchial disease, one cannot help but reflect upon the possible role played by the glands of the esophagus, especially the deep or mucous type glands as compared to the superficial or cardiac type. These glands can be seen with the naked eye in the opened esophagus dotting the mucous membrane as small punctate openings. If altered as the result of a low grade inflammatory process perhaps they might dilate or hypertrophy to become the diverticula here demonstrated.

In this regard one cannot entirely disregard the possibility that intramural esophageal diverticula are related to esophageal moniliasis. Despite the fact that neither patient had debilitating disease treated with antimicrobial or cellular toxic drugs, they might have had an unnoticed esophageal moniliasis in the past which left them with esophageal residue. The possibility is here entertained because moniliasis characteristically causes diffuse esophageal ulceration, granularity and irritability as recorded by Andren and Theander, Kaufman, Scheff and Levene,2 as well as Marsh.3 Moniliasis could conceivably have led to the intramural diverticula; certainly, it would explain the esophageal irritability.

CONCLUSIONS

- 1. Report of a second patient with intramural esophageal diverticulosis is added to the literature.
- 2. Intramural esophageal diverticulosis is associated with dysphagia.
- 3. Intramural esophageal diverticulosis may be related to old esophageal inflammation or congenital abnormalities.

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ADDENDUM

A third patient with intramural esophageal diverticulosis was seen by Dr. Richard Schatzki of Harvard Medical School, Boston, Massachusetts. This patient's roentgenograms were sent to him from Havana, Cuba, by Dr. R. Hernandez Beguerie in 1954. Dr. Schatzki, too, believes that these diverticula could represent dilatation of the esophageal mucous glands.

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PENETRATING WOUNDS OF THE ABDOMINAL WALL*

A NEW DIAGNOSTIC TECHNIQUE

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PENETRATING wounds of the ab-dominal wall represent a difficult diagnostic problem to the clinician regarding the presence or absence of intra-abdominal injury. Immediate exploratory laparotomy has usually been advised to determine if any injury has occurred to the abdominal contents. This method of treatment has prevented most of the complications of penetrating abdominal wounds, but has resulted in a large number of unnecessary operations. At the Johns Hopkins Hospital during the past 10 years, only 40 per cent of abdominal stab wounds were shown at the time of surgery to have penetrated. In the present report a technique is described by which it can be determined whether penetration into the abdominal cavity has occurred.

METHOD

The procedure was carried out in each case in the Emergency Room, using standard roentgenographic equipment. The area around the stab wound is prepared with septisol and aqueous zepharim to establish a sterile field. A number 14 French catheter is inserted through the skin wound into the subcutaneous tissue without making any attempt to find the tract or to pass the catheter directly into the peritoneal cavity. The skin edges are secured tightly around the catheter with a purse string suture of oo-silk. Sixty to eighty cubic centimeters of sodium diatrizoate (hypaque 50 per cent) with 1 cc. of methylene blue is injected into the catheter under careful observation to be certain that the solution does not leak out of the wound onto the abdominal wall. The catheter is then clamped and abdominal roentgenograms are made. Both anteroposterior and lateral studies are obtained in the recumbent position. When necessary, oblique views of the abdomen are included to clarify the location of contrast material.

In order for a study to be considered satisfactory, it is necessary for a large opaque area of contrast material to be seen on the roentgenogram (Fig. 1, A and B). This diffusion of contrast material demonstrates

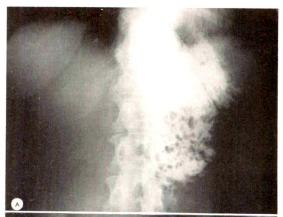




Fig. 1. (A) Anteroposterior roentgenogram of the abdomen demonstrating a large subcutaneous collection of contrast material. (B) Lateral abdominal roentgenogram in the same patient revealing that the contrast material is confined to the abdominal wall and does not enter the peritoneal cavity. (Reproduced with permission of J. Surg. Res.1)

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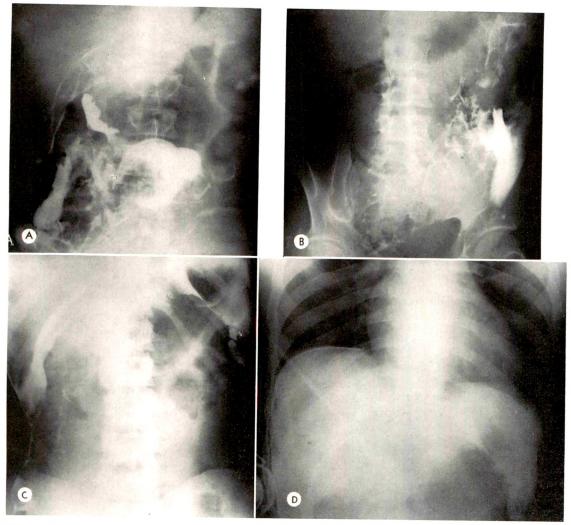


Fig. 2. (A) Anteroposterior roentgenogram of the abdomen in recumbent position demonstrating a large quantity of contrast material in the peritoneal cavity, outlining the large and small bowel and the under surface of the liver and (B) the splenic flexure. (C) Contrast material outlining the right lateral peritoneal reflexion and undersurface of the liver and (D) contrast material around the liver as well as the spleen and splenic flexure of the colon.

strates that a sufficient quantity is injected to follow the tract of the penetrating injury and enter the peritoneal cavity, if such an opening exists (Fig. 2, A-D; and 3, A and B). The methylene blue is added to permit recognition at the time of laparotomy and to facilitate interpretation of the roent-genograms.

RESULTS

To the present time, the study has been performed in 40 patients. In one patient

early in the series the study was considered unsatisfactory for interpretation. All 12 patients with roentgenographic evidence of contrast material in the peritoneal cavity had a definite laceration of the peritoneum at the time of laparotomy. None of the 10 patients whose test was interpreted as negative for penetration into the abdominal cavity had perforation of the peritoneum at operation. There were 18 patients who had no roentgenographic evidence of contrast material entering the peritoneal cavity

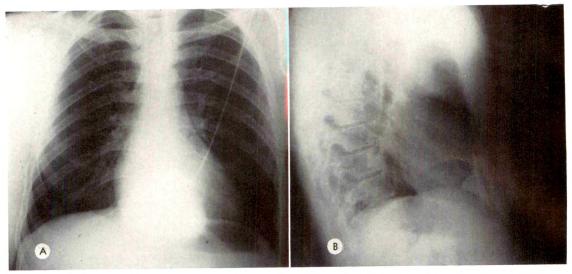


Fig. 3. Patient stabbed just above the diaphragm with an ice pick. Injection of contrast material demonstrated in the (A) anteroposterior and (B) lateral roentgenograms that neither the peritoneum nor the pleural spaces were entered. The hypaque is confined to the anterior mediastinum.

that did not have laparotomy. These patients had no clinical evidence of intraabdominal injury and were discharged after 48 hours of observation. None of these patients showed late evidence of injury.



Fig. 4. Abdominal roentgenogram following injection of stab wound. The contrast material did not enter the peritoneal cavity and is seen in the renal collecting system (arrows).

COMMENT

There have been no adverse effects such as infection or necrosis of the underlying tissues following injection of sodium diatrizoate into the wounds. Patients complained of minimal discomfort at the time of injection. The material is completely absorbed from the tissues in 36 hours. Opacification of the renal collecting system is usually seen on the roentgenograms, indicating the rapidity in which the contrast material is absorbed (Fig. 4). There have been no false negative or false positive interpretations of the test to date. The study was considered unsatisfactory in one patient early in the series. If the study is positive for penetration of the peritoneum or not satisfactory for interpretation, immediate exploratory laparotomy is performed. Although we have encountered no false negative examinations to date, it is our practice to carry out early exploration in all patients with penetrating abdominal wounds. If these early results are borne out in our continuing experience, it may be possible to carry out a more conservative program of management in patients with negative studies.

SUMMARY

On the basis of preliminary results obtained by injection of wounds with radiopaque contrast material, we can state that failure to demonstrate penetration of the peritoneal cavity is strong evidence that the peritoneum is not punctured. This is a continuing study and a full evaluation of a more extensive experience will be the subject of a subsequent report. The technique as described is simple to perform, safe for the patient, appears to be reliable and is

another example of the value of diagnostic roentgenographic techniques in the treatment of the acutely injured patient.

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SPLENIC CYSTS: CONFIRMATION BY SELECTIVE VISCERAL ANGIOGRAPHY*

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CYSTS of the spleen are rare, and as a result, little is known of their true incidence, etiology, propensity to cause symptoms or indication for treatment. In 1956, Posener and Litherland⁵ were able to collect only 211 cases of splenic cysts from the literature. Most of these had been discovered because of pressure symptoms on the adjacent viscera. The preoperative diagnosis, therefore, generally rested upon indirect evidence of encroachment on neighboring structures as demonstrated by roentgenograms. However, the diagnosis has been circumstantial at best.

The purpose of the authors is to report the diagnosis of a splenic cyst by selective visceral angiography and to discuss the potential value of this method.

REPORT OF A CASE

This 50 year old patient was admitted to the VA Hospital because of severe facial contusions. A past alcoholic history was elicited with many incidents of trauma. A survey roentgenogram of the abdomen demonstrated a large calcified mass in the left upper quadrant. Intravenous pyelography, examination of the upper and lower gastrointestinal tract and physical examination confirmed the mass. Exact localization was questioned and, consequently, vascular angiography was recommended.

A pre-formed Ödman-Ledin green catheter was inserted by femoral percutaneous technique and introduced into the left renal artery. Eight cubic centimeters of 60 per cent renografin was injected at a flow rate of 10 cc./sec. Programming included the arterial, nephrographic and venous phase (Fig. 1; and 2, A and B). The calcified cyst was extrarenal and compressed the upper pole of the kidney. The

catheter was then inserted into the celiac axis and 20 cc. of 60 per cent renografin was injected at a flow rate of 15 cc./sec. The splenic vessels were displaced by the avascular cyst and a section of the splenic parenchyma was replaced by the cyst as shown in the capillary and venous phase angiograms. Because of the prominent transverse and caudal pancreatic branches, there was intense filling of the tail and body of the pancreas (Fig. 3, A, B and C).

DISCUSSION

Since most reports of cysts of the spleen deal with the patient who has had symp-



Fig. 1. A large calcified cystic mass is present in the left upper quadrant.

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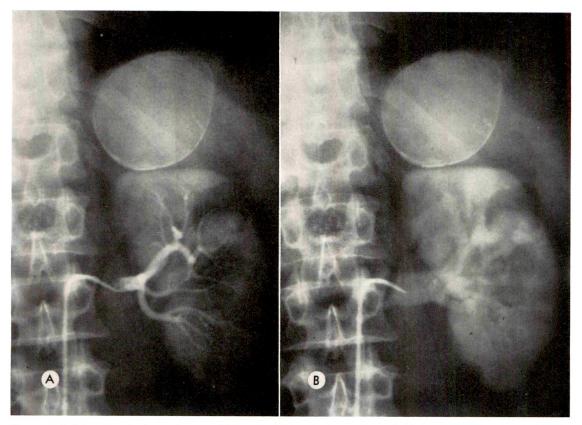


Fig. 2. (A) Selective renal arteriogram demonstrating normal renal vasculature. There is no tumor circulation visible and the inferior adrenal is not filled. (B) Nephrographic and venous phase show compression of the upper pole of the kidney by the extrarenal mass. Note the normal renal vein. (A reproduced with permission from Surg., Gynec. & Obst.6)

toms, the true incidence, life history and indications for surgery are not yet known. Gipson et al.4 have stressed the importance of a hemorrhagic cyst which resulted from prior infectious mononucleosis and its tendency to rupture. Allen and Condon¹ reported 3 cases of splenic cyst in children and pointed out the indirect roentgen findings: displacement of the stomach or colon or kidney. While these signs may be present in a varying percentage of cases, they still do not establish the diagnosis of a splenic cyst with certainty. The differential diagnosis of a mass in the left upper abdominal quadrant must include tumors of the pancreas, stomach, colon, adrenal, kidney, and aneurysms of the celiac axis vessels. Once it has been established that the mass arises in the spleen, then the type of enlargement must be decided upon.

The introduction of percutaneous selective vascular examinations has opened new vistas of diagnostic possibilities. The application of this method for the study of visceral organs has been reviewed recently by Wholey, Eisen and Poller⁶ and Bøijsen and Bron.² With the greater application of selective visceral angiography, cysts of the spleen, both symptomatic and asymptomatic, as well as more uncommon clinical entities will be discovered. Various neoplasms, infectious granulomas, arteriovenous malformations as well as traumatic hematomas of the spleen can now be well delineated by this method. The value of visualizing the splenic and portal venous system following celiac axis and superior mesenteric artery injection and the evaluation of flow patterns in portal hypertension as well as thrombosis from adjacent neo-

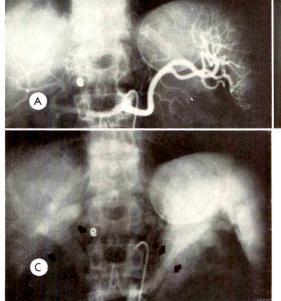




Fig. 3. (A) Selective celiac axis arteriogram in the early arterial phase demonstrating some displacement of the splenic vessels laterally. (B) Same injection in a later arterial phase now demonstrating the stretched splenic vessels. Note the large caudal and transverse pancreatic branches. No tumor circulation is present. (C) The venous phase demonstrating the large avascular cyst to occupy the medial portion of the spleen with displacement of the splenic structure laterally. Note the intense filling of the body and tail of the pancreas with no displacement of the pan-

creatic structures. The splenic vein and portal vein are visible as the contrast medium returns from the splenic parenchyma. There is no involvement of the splenic or portal vein. (A reproduced with permission from Surg., Gynec. & Obst.6)

plasms have been established.³ Serial angiographic studies of these lesions seem to offer a unique opportunity towards a better understanding of their clinical behavior and may help establish a firm rational basis for their proper treatment.

SUMMARY AND CONCLUSIONS

A case of solitary cyst of the spleen is reported.

Availability of visceral angiography affords the surgeon, radiologist and internist an opportunity to study the nature of this entity before proceeding with a definitive mode of therapy.

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NONPARASITIC CYSTS OF THE LIVER*

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THE presence of a nonparasitic cyst of the liver constitutes an uncommon and relatively benign condition which may assume an important role in the differential diagnosis of intra-abdominal mass lesions.

Stoesser and Wangensteen recorded 104 cases in 1929, and 30 years later Morgenstern⁶ was able to increase the total number of reported cases to 250. In a series of 28,000 consecutive autopsies. Eliason and Smith² found only 28 cases of hepatic cyst and in no instance was the diagnosis suspected premortem. The same authors reported 2 correct antemortem diagnoses in 211,046 admissions to their institution.

ETIOLOGY AND CLASSIFICATION

The most widely accepted classification is that of Jones:

- 1. Cystadenomas (proliferative cysts)
- 2. Pseudocysts (degenerative cysts)
- 3. Teratomatous (embryomatous or dermoid) cysts
- 4. Lymphatic (lymphangiomatous) cysts
- 5. Endothelial (ciliated epithelial) cysts
- 6. Blood vessel (hemangiomatous) cysts
- 7. Bile duct (retention) cysts

Multiple cysts of the liver are commonly associated with cystic changes in other organs and are, therefore, classified by most authors as part of polycystic disease. This concept is complicated, however, by the occasional finding of adjacent smaller cysts in proximity to a larger dominant cyst. The question still remains unsettled as to whether the purely solitary hepatic cyst represents a single manifestation of polycystic disease or is entirely unrelated. 3,8

Etiologic factors which have been implicated in the formation of hepatic cysts include congenitally obstructed or aberrant bile ducts with cystic dilatation^{6,7} and

localized injury or inflammation with bile duct and/or lymphatic obstruction.³ More recently, the analogy with respiratory malformations originating from the embryonic foregut has been presented.¹ Neoplastic transformation of epithelial tissue and localized degenerative changes resulting from hemorrhage, infection, or trauma have also been suggested.³

PATHOLOGY

Grossly, the cysts will vary from a few millimeters in diameter to an enormous size, capable of filling the entire abdomen. The right lobe is involved twice as often as the left, and the cyst most commonly occupies the anterior under-surface of the liver. The presenting external surface of the cyst is usually smooth, glistening and grayish blue in color. The cyst may be entirely intrahepatic, or may be attached to the liver by a stalk of varying size. The internal surface of the cyst is usually smooth and often trabeculated with a lining wall of varying thickness, poorly demarcated from the surrounding normal hepatic parenchyma. The cyst contents vary from clear, yellowish serous fluid to dark, viscid and semi-solid material. This substance is composed of cholesterol, hemic elements, cellular debris, mucin, and, rarely, bile. Microscopically, the cysts are composed of 3 separate layers. There is an inner, richly cellular laver, a circularly arranged dense connective tissue middle zone, and finally, a loose outer layer containing numerous elastic fibers, blood vessels, muscle bundles and scattered bile ducts.

CLINICAL FINDINGS

Hepatic cysts occur in females 4 times as frequently as in males. They have been reported in all age groups, but most com-

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monly are detected in the fourth to fifth decade. The majority of patients are asymptomatic or complain of nonspecific and variable symptoms. The slow growth of these lesions produces gradual pressure on adjacent viscera so that the commonest complaint is that of vague abdominal discomfort, usually associated with painless abdominal enlargement. The sudden onset of acute symptoms may result from torsion of a pedunculated cyst or may indicate hemorrhage, inflammation and/or perforation of the cyst. Icterus is rare and, when present, is usually of the obstructive type, secondary to compression of the extrahepatic bile ducts by the cyst.4 Pyloric or intestinal obstruction occurs rarely, and is produced by similar extrinsic pressure.

Physical examination may demonstrate an upper abdominal mass of varying size which is contiguous with the liver. The patient's general health and well-being usually are unaffected; a state of affairs sharply in contrast to the large abdominal swelling. If lateral mobility of the cyst is present, it probably is of the pedunculated variety. Laboratory data are unremarkable, and liver function tests almost always are within normal limits.

CLINICAL MATERIAL

All of the 5 patients in our series were females, and ranged in age from 48 to 70 years. In 4 of these patients, abdominal discomfort was the major complaint which varied from a mild feeling of fullness to considerable pain. The fifth patient was asymptomatic, and the cyst was discovered at the time of hospital admission for an unrelated complaint.

Laboratory studies, including liver profile, were all within normal limits.

Because of the difficulty in establishing a definite preoperative diagnosis, all the patients underwent exploratory laparotomy.

ILLUSTRATIVE CASES

CASE I. F.S., a 49 year old woman, was admitted to Montefiore Hospital with a history

of 3 episodes of sharp right upper quadrant pain radiating to the back. There was a vague history of fried food intolerance, but the patient denied icterus or vomiting. A cholecystogram performed prior to admission had demonstrated 3 calculi in the gallbladder.

On physical examination, a soft tender mass was palpable beneath the right costal margin. Laboratory examination showed a hemoglobin of 11 gm., a white blood cell count of 4,500 and normal urinalysis.

Two days after admission, the patient underwent an exploratory laparotomy, and numerous cysts were noted to be present throughout the substance of the right liver. These varied in size from 2 to 3 inches in diameter to that of a pin head. Several cysts were aspirated, and the sacs and capsules were excised. The gallbladder itself was thought to be normal but was not opened. Sections of the cyst walls disclosed dense fibrous tissue containing prominent islands of intact liver parenchyma. No biliary stasis was evident, and occasional prominent bile ducts were noted. The cyst lining was composed of flat and cuboidal epithelium.

The final histologic diagnosis was cystic disease of the liver.

Case II. This 62 year old woman was admitted to Montefiore Hospital with upper abdominal pain for 3 months and a history of "belching" for several years.

On physical examination an irregular mass, thought to be cystic, was noted in the epigastrium, extending to between 5 to 8 cm. below the right costal margin. The mass was slightly tender to palpation.

Laboratory examination was noncontributory.

Upper gastrointestinal series demonstrated an extrinsic pressure type defect on the anterior lesser curvature aspect of the stomach (Fig. 1 and 2).

At surgical exploration, the left lobe of the liver was smoothly enlarged and deformed by a grapefruit-sized cyst which involved the posterior and ventral surfaces of the liver. The right lobe of the liver, the stomach, colon, and gallbladder were free of disease. The cystic structure, containing 150 cc. of brownish fluid, was removed.

The cyst measured 10 cm. in diameter. The wall was multiloculated and lined by cuboidal epithelium. Some of the cells contained bile pigment. There was no evidence of malignancy.

The final diagnosis was nonparasitic multiloculated cyst of the liver.

Case III. A.M., a 67 year old woman, was admitted to Montefiore Hospital complaining of upper abdominal pain and gaseous eructations for the past several years, and a feeling of fullness in the right side of the abdomen for several months.

On physical examination, there was no abnormality with the exception of a soft, smooth right upper quadrant mass which was spheroid and extended 4 fingers below the right costal margin. The mass appeared to move with respiration.

Laboratory examination demonstrated a hematocrit of 35 per cent, 4,900 white blood cells and a normal differential. Liver chemistries showed an alkaline phosphatase of 1.4 Bodansky units, thymol turbidity 2 units, cholesterol 224 mg. per cent, and a prothrombin time of



Fig. 1. Case II. Anteroposterior roentgenogram of the abdomen, upper gastrointestinal study. There is a large, smooth, extrinsic pressure defect along the lesser curvature of the barium filled stomach.



Fig. 2. Case II. Erect lateral roentgenogram of the abdomen, upper gastrointestinal study. There is no posterior displacement of the stomach such as would be produced by a pancreatic or retroperitoneal tumor.

11.2/11 seconds. The other laboratory data, including serum electrophoresis, were noncontributory.

An I¹³¹ rose bengal hepatogram (performed by Dr. Abraham A. Sherman) showed 2 areas of decreased uptake, one in the lowermost portion of the right lobe and a second smaller area in the upper part of the right lobe beneath the diaphragm.

Roentgen examination of the chest and skull was normal, and an intravenous pyelogram showed no abnormality. An upper gastro-intestinal series was normal except for a deformed duodenal bulb. An intravenous cholangiogram showed evidence of a nonobstructing mass impinging on the superior pole of the gallbladder (Fig. 3).

On surgical exploration, 2 hepatic cysts were encountered. The clinically palpable cyst was noted on the inferior border of the liver, just lateral to the falciform ligament. It contained about 50 cc. of sterile, clear, white fluid. The second cyst was felt on the upper anterior sur-



Fig. 3. Case III. Left anterior oblique intravenous cholangiogram. There is a smooth pressure type defect on the superior portion of the contrast filled gallbladder. The biliary ductal system is normal.

face, embedded within liver substance. The gallbladder was slightly enlarged but otherwise normal.

The clinically palpable cyst was opened and partially excised. A liver biopsy was also performed.

Microscopic examination of the cyst wall showed a portion of connective tissue containing bile ducts, scattered groups of liver cells, numerous small blood vessels, and collections of inflammatory cells (Fig. 4, A and B).

The final histologic diagnosis was simple cyst of the liver. Liver biopsy showed bile duct hamartoma and increased amounts of iron pigment.

Case IV. J.P., a 49 year old female, was admitted to Montefiore Hospital with a presenting complaint of cough, fever, vaginal bleeding and dysuria. The patient had been admitted 6 months previously for treatment of pneumonitis, and at that time an enlarged liver was noted, which was biopsied and showed no abnormality.

On physical examination, the liver showed evidence of progressive enlargement, and was now palpated 5 fingers below the right costal margin as compared with a previous 2 finger breadth enlargement. The patient also demonstrated bilateral costovertebral tenderness.

Three days after admission, the patient underwent uterine dilatation and curettage which demonstrated an atrophic endometrium. Two days later, a liver biopsy was attempted which failed to obtain sufficient tissue for a diagnosis. Serous fluid was aspirated at this time and air was then introduced prior to obtaining roentgenograms of the abdomen.

Laboratory examination demonstrated marked pyuria with cultures positive for *E. coli*. Liver chemistries were as follows: Alkaline phosphatase 2.6 Bodansky units, transaminase 19 units, bilirubin 0.38, cephalin flocculation 2+, albumin/globulin ratio 3.5/3.3.

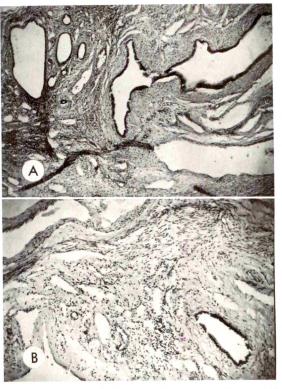


Fig. 4. Case III. (A) Microscopic section of cyst wall (65× magnification) showing connective tissue with cellular infiltrate and small blood vessels. The cyst wall is composed of columnar epithelium as well as flattened epithelial cells in some areas. (B) Microscopic section of cyst wall (130× magnification) showing the features described in A, especially the fibrous stroma with cellular infiltration.

Roentgenologic examination of the chest showed further elevation of the right diaphragmatic leaflet as compared with an examination 6 months previously, consistent with an enlarging liver (Fig. 5). Plain roentgenograms of the abdomen demonstrated a soft tissue subdiaphragmatic mass on the right with air fluid levels (Fig. 6, A and B). On excretory urograms, the right kidney appeared depressed, but was otherwise normal (Fig. 7). Barium enema examination demonstrated depression of the hepatic flexure (Fig. 8, A and B).

The patient did well, thereafter, and was discharged at her request, to be followed as an out-patient. She then returned to the hospital 6 months later for elective surgical exploration because of progressive hepatic enlargement. At this time, the liver was palpable 8 fingers below the right costal margin and described as firm.

Surgical exploration demonstrated a large hepatic cyst from which about I liter of straw colored fluid was aspirated. Several very small cysts were noted adjacent to the large cyst; it was possible to excise 3 such cysts.

On pathologic section, the larger cyst wall was composed of a layer of mesothelial cells and, beneath this, a layer of collagenous tissue. The largest diameter of the cyst wall contained many structures resembling cholangioles, and individual hepatic cells could also be identified.

The cysts were considered to be probably hamartomatous in origin with a predominant bile duct component.

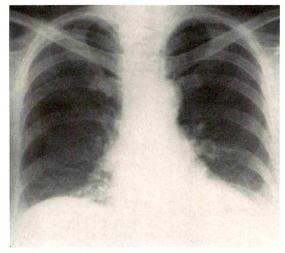
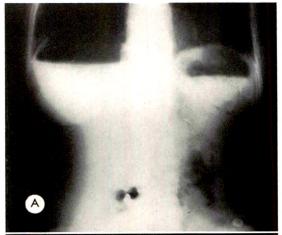


Fig. 5. Case IV. Posteroanterior roentgenogram of the chest. There is elevation of the right diaphragmatic leaflet with rounding of the upper margin. The lungs are clear.



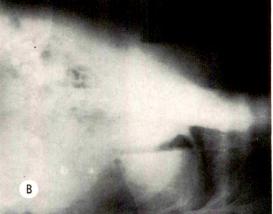


Fig. 6. Case IV. (A) Posteroanterior erect examination of the abdomen. The contents of the hepatic cyst have been partially aspirated and replaced with air. A large right subdiaphragmatic air-fluid level is present outlining the transverse diameter of the cyst. (B) Left lateral decubitus (horizontal beam) examination of the abdomen. The large right upper quadrant air-fluid level outlines the margins of the cyst.

Case v. A.L., a 70 year old woman, was admitted to Montefiore Hospital with a 10 month history of fullness in the abdomen. Six months prior to this admission, the patient began to note occasional right upper quadrant discomfort, as well as a feeling of satiety after meals. The right upper quadrant became increasingly firm and sensitive. An intravenous pyelogram made 19 days prior to admission demonstrated extrinsic pressure on and downward displacement of the right renal pelvis.

Physical examination disclosed a large, firm right upper quadrant mass, moving with respiration, and having a sharply defined lower border.



Fig. 7. Case IV. Anteroposterior roentgenogram of the abdomen, intravenous urogram. There is caudal displacement of the right kidney. The collecting system is normal.

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The remainder of the examination was within normal limits.

Laboratory examination showed a normal blood cell count, blood urea nitrogen and fasting blood sugar. Urinalysis was negative except for 6 white blood cells per high power field. Calcium and phosphorus determinations were normal. Liver chemistries showed an alkaline phosphatase of 2.1 Bodansky units, and a transaminase of 28 units.

Intravenous aortography showed an avascular mass displacing the hepatic and renal arteries on the right, and also a pressure defect on the right side of the aorta (Fig. 9). A right retrograde pyelogram following presacral air insufflation showed an extrarenal mass which

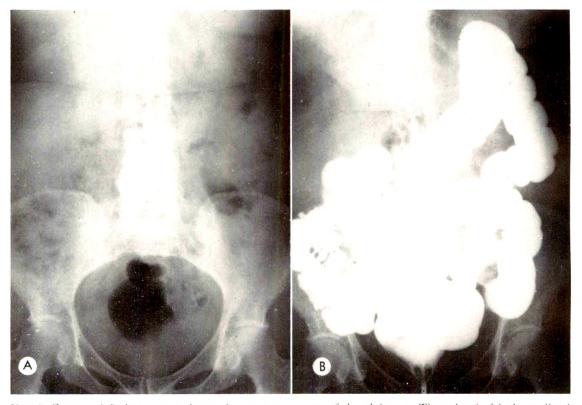


Fig. 8. Case IV. (A) Anteroposterior supine roentgenogram of the abdomen. The colon is faintly outlined by retained gas and fecal matter. The hepatic flexure appears depressed. (B) Anteroposterior barium enema roentgenogram. The plain film impression of hepatic flexure depression is confirmed. The colon is intrinsically normal.

did not appear to be retroperitoneal in origin (Fig. 10).

Four days later, an exploratory laparotomy was performed and a huge cyst of the right lobe of the liver was encountered, containing approximately 2 quarts of brownish fluid. Several smaller cysts were noted in the left lobe of the liver. The right liver edge appeared to be necrotic from possible compression. A hard mass was noted in the head and body of the pancreas which had the appearance of a carcinoma.

Pathologic description of the cyst wall and liver indicated fibrocollagenous connective tissue containing ducts of various sizes. Islands of liver parenchyma were seen, but no mitotic figures. Other sections showed dense collagenous connective tissue with lymphocytic and plasma cell infiltration. The biopsy from the pancreas revealed an adenocarcinoma presumably arising from this organ.

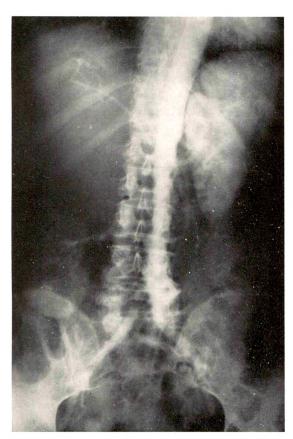


Fig. 9. Case v. Intravenous aortogram, anteroposterior projection. The hepatic artery is stretched superiorly and bowed upward by an avascular mass. The right kidney and renal artery are displaced inferiorly.



Fig. 10. Case v. Combined presacral air insufflation and right retrograde pyelogram. The right kidney with its collecting system is depressed and flattened by an extrarenal mass which is not of retroperitoneal origin.

The final diagnosis was liver cyst and adenocarcinoma of the pancreas. It should be noted that the carcinoma was not suspected, and had no obvious connection to the cystic disease of the liver.

ROENTGEN FEATURES

Plain roentgenograms in cases of uncomplicated hepatic cyst may show an upper abdominal soft tissue mass with no clear delimitation from the hepatic shadow. The right diaphragmatic leaflet is elevated with diminished respiratory excursion. In the lateral projection, such elevation may be more marked anteriorly, suggesting hepatic enlargement. There generally is no evidence of an associated pleural reaction or infrapulmonary effusion, and the inferior portion of the right lung is normal with the possible exception of segmental hypoventilation related to the high diaphragmatic leaflet. If the hepatic flexure is outlined by intraluminal gas or feces, it will always

appear depressed, and may be deviated to the left.

Barium enema examination confirms the impression of downward displacement of the hepatic flexure. The hepatic flexure is not displaced forward as might occur with a retroperitoneal mass. Barium meal opacification of the stomach and duodenum will demonstrate evidence of an extrinsic pressure deformity on the duodenum and antrum of the stomach, and these organs as well as the small bowel are usually displaced to the left. If the cyst occupies primarily the left lobe of the liver, the anteroposterior projection of the stomach may show changes similar to those produced by a pancreatic cyst. The lateral projection however, usually will confirm the anterior location of the mass, thereby excluding a pancreatic origin.

The gallbladder and biliary ductal system may also show various extrinsic pressure defects depending on their positional relationship to the hepatic cyst. Excretory urography may show caudal displacement of the right kidney, but will be otherwise unremarkable. Pneumoperitoneum is rarely of diagnostic value.

Abdominal aortography may show stretching and distortion of the hepatic artery with no increased or abnormal vascularization; there may be a corresponding avascular zone in the hepatogram phase.

Needle puncture of the cyst with installation of gas or contrast material will clearly define the size and extent of large cystic cavities.

Radioactive liver scan with I¹³¹ rose bengal or radioactive gold will show areas of decreased uptake corresponding to the cyst, and may, therefore, give an indication as to size and number. In such instances, of course, primary or secondary neoplastic masses cannot be excluded.

THERAPY

Total excision, if feasible, is the definitive treatment of choice. Other modes of therapy include partial excision with suture obliteration of the cavity, marsupialization, internal drainage and the use of sclerosing agents. If the cysts are asymptomatic and a definite diagnosis can be established, surgery should not be necessary.

SUMMARY AND CONCLUSIONS

- 1. Five cases of solitary, nonparasitic cyst of the liver are reported.
- 2. The incidence, classification, pathologic nature, clinical manifestations and roentgen diagnosis of this entity are discussed.
- 3. The finding clinically and by roentgen examination of a solitary right upper quadrant mass of water density, displacing the adjacent viscera in an appropriate way (as described) in a relatively healthy patient should suggest the diagnosis of hepatic cyst.
- 4. Radioactive liver scanning and abdominal aortography, though not diagnostic, may be helpful.

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CARCINOMA OF THE BODY AND TAIL OF THE PANCREAS*

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In THIS report the roentgen features in 46 patients with carcinoma of the body and tail of the pancreas are described and analyzed.

As the pancreas resists direct visualization, the roentgen diagnosis depends primarily upon barium studies. Changes demonstrated in juxtapancreatic viscera indicate direct or indirect involvement by the advancing neoplasm.

Pancreatic neoplasms are discussed usually in terms of ampullary lesions. Carcinomas of the body and tail are generally considered rare occurrences. 6,10 Data compiled from several publications, however, indicate that 25 per cent of 370 consecutive pancreatic carcinomas were confined to the body and tail. 4,9,30,32

BACKGROUND

Pancreatic neoplasms have been reported as comprising 0.85 per cent of all carcinomas. 1,7,9,15,26,31 These figures represented 0.5 per cent of all hospital admissions²⁷ and 0.51 per cent of 13,500 consecutive necropsies. 2,8,9,12,13,15,16 The disease predominates in males, with a ratio ranging from 2:1 to as high as 7:1. 8,28 No predilection to race was observed. The average age of patients in whom the disease occurred varied from 55 to 58 years. Approximately 60 per cent of the patients were between the ages of 50 and 69 years. The disease has been reported in patients as young as 20 years of age. 12

The cause of pancreatic carcinoma is unknown. The growths are usually primary and rarely metastatic. The cell type is predominantly adenocarcinoma which, in most cases, arises from ductal epithelium. This neoplasm is characteristically scirrhous.

Occasionally, the origin is acinar tissue, producing soft, bulky tumors.¹² Strang and Walton³⁰ reported that in 58 patients with carcinoma of the body and tail of the pancreas, the average duration of symptoms before hospitalization was 4.5 months. In the same series, the average duration from onset of symptoms to death was 7 to 8 months.

The prognosis for malignant tumors of the pancreas is grave for the following reasons:

- (a) Nature of the process. The onset of the neoplasm is insidious. The growth is relentless and is only rarely controlled surgically.
- (b) Inability to establish early diagnosis. The peculiar location of the pancreas permits growth without early clinical symptoms. Even involvement of adjacent structures often produces no symptoms.
- (c) Propensity to early and massive extension. The pancreas has no limiting capsule and only the thin peritoneum is interposed between it and the cavity of the lesser sac. Once this barrier is penetrated, generalized abdominal metastasis may occur. Furthermore, the venous and lymphatic drainage of the pancreas is unusually rich.

Clinically, the principal signs and symptoms are weight loss, weakness, fatigue, and abdominal pain. These common symptoms rarely permit the correct diagnosis despite energetic investigations. 9.11,17,18,25,26,28,32 Pancreatic neoplasms, as a rule, do not sufficiently disrupt pancreatic function to permit laboratory detection.

MATERIALS AND METHODS

The records of 46 patients with car-

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Table I

SEX AND AGE OF 46 PATIENTS WITH PROVED CARCINOMA OF THE BODY AND TAIL OF PANCREAS

	46
29 (63%)	
17 (37%)	
	63.3 years*
64.3 years	
61.7 years	
	17 (37%) 64.3 years

^{*} Ages ranged from 25 to 78 years.

cinoma of the pancreas involving the body or tail, or both, were reviewed. These patients were seen at the University of California Medical Center, San Francisco, between January, 1955 and April, 1964. Males predominated with a ratio of 1.7:1. The sex and age distributions of the present series are shown in Table 1. The diagnosis was proved by necropsy or laparotomy in all cases. In 57 per cent of the patients, the tumor was confined to the body of the pancreas, but involvement of the body along with the tail was present in 85 per cent (Table II).

Gastrointestinal roentgen examinations, combined with numerous other roentgen studies totaled 87 (Table III). An upper gastrointestinal series was combined with a barium enema examination in 21 patients, whereas the upper gastrointestinal series alone was obtained in 18.

The projections used for routine upper gastrointestinal roentgenograms in this department are supine anteroposterior, prone posteroanterior, prone right anterior oblique, and overhead right lateral, together with appropriate spot roentgenograms. All roentgenograms, including plain

Table II

LOCATION OF TUMORS IN 46 CASES OF CARCINOMA
OF THE BODY AND TAIL OF THE PANCREAS

Body Body and tail Tail	26 (57%) Body involved in 85 per 13 (28%) cent 7 (15%)
Total	46 (100%)

films, were examined by the authors and abnormal findings were recorded as "definite" or "suspicious." Since this was an entirely retrospective study, no attempt was made to test diagnostic accuracy. After the initial review of all roentgenograms and the recording of findings, the roentgenograms were reinterpreted by each author, without knowledge of the previous interpretations, and findings were again recorded. This procedure was repeated a third time. Finally, all three interpretations were compared and only those abnormalities termed "definite" or "suspicious" each time were accepted.

A careful scrutiny was then made of a control group of 200 consecutive upper gastrointestinal roentgenograms, searching for the same changes that were considered characteristic of carcinoma of the body and tail of the pancreas. Occasionally, the appearance of the stomach or duodenum on a single view was suggestive of this disease, but the changes were not consistent when the entire examination was reviewed. In assessing the roentgenograms of the control group, abnormalities suggesting carcinoma of the body or tail of the pancreas, or both, were noted in I patient. At surgery, carcinoma of the body of the pancreas was present. This patient subsequently became the forty-sixth subject of the present study.

Table III
ROENTGENOLOGIC EXAMINATIONS PERFORMED

Type of Examination	No. of Patients	Per Cent of 46 Patients
Esophagram	3	, may
Upper gastrointestinal	40)	•
series, I time		
Upper gastrointestinal	2 .44	96
series, 2 times		
Upper gastrointestinal	2	
series, 3 times)	
Small bowel series	5	1.1
Barium enema, 1 time	21	
Barium enema, 2 times	1 24	52
Barium enema, 3 times	2	-
Gallbladder	12	26
Intravenous pyelogram	20	4.3

ROENTGEN FEATURES

Roentgenographically, the changes manifested by carcinomas of the body and tail of the pancreas are primarily reflected by deformities of the barium-filled gastrointestinal tract. The gut, being relatively soft and pliant, permits impressions and invasion by the advancing neoplasm. In roentgenograms of the upper gastrointestinal tract in suspected carcinoma of the pancreas, the gastric antrum and descending duodenum are usually closely examined for evidence of carcinoma of the pancreatic head. Only scant attention is given to the body and fundus of the stomach or to the third and fourth portions of the duodenum. In the present study, these were the areas in which neoplasms of the body and tail of the pancreas predominantly produced their abnormalities.

GASTROINTESTINAL MANIFESTATIONS

Esophagus. Although we did not find esophageal abnormalities, it is well documented that the esophagus may be affected by neoplasms of the body and the tail of the pancreas.^{27,30}

Stomach. The stomach is a sling of alimentary canal fixed proximally by the cardioesophageal junction and at the gas-

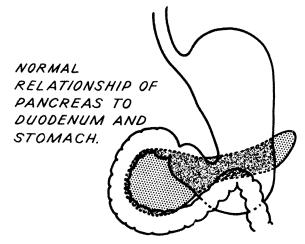


Fig. 1. Note how lesions of the tail of the pancreas could involve the upper gastric body and fundal areas while lesions of the body of the pancreas are proximate to the gastric antrum, gastric body, and the duodenojejunal junction.

TABLE IV

GASTRIC ROENTGEN FINDINGS IN 46 CASES OF CARCINOMA OF BODY AND TAIL OF PANCREAS

Roentgen Findings	No. of Times Occurred	Description	Mary and a second
Displacement	31*	Right	2
	(67%)	Left	
		Superior	, 5
		Inferior	7 5 2
		Anterior	25
Invasion	19 [†] (41%)	Fixation of wall with intact mucosa and/or edema	11
		Destruction of mu- cosa and/or ulceration	12
		Obstruction, partial or complete	0
Extrinsic mass		Impression defect	30
	(67%)	"Splaying" of mucosal folds	6

^{*} In several instances displacement occurred in more than one direction.

troduodenal region by the peritoneum. Because its location is relatively stationary, its various portions remain in a somewhat constant relationship with the underlying pancreas (Fig. 1). Thus, lesions in the head of the pancreas tend to produce antral deformities, whereas those of the body produce deformities in the body of the stomach. Fundal changes may result from lesions of the tail (Fig. 2, A-F). For this study, the gastric findings were divided into three categories: displacement; impression by extrinsic mass; and invasion (Table IV).

Displacement of the stomach was found 31 times in this series, the result of impression by tumor mass (Fig. 3, A-E). The displacement was anterior in 25 (Fig. 2D). The area most often involved was the body of the stomach or the body and antrum combined. Since 85 per cent of the neoplasms

[†] Three cases revealed fixation and destruction of mucosa. ‡ All 6 with "splayed" mucosal folds also had impression de-

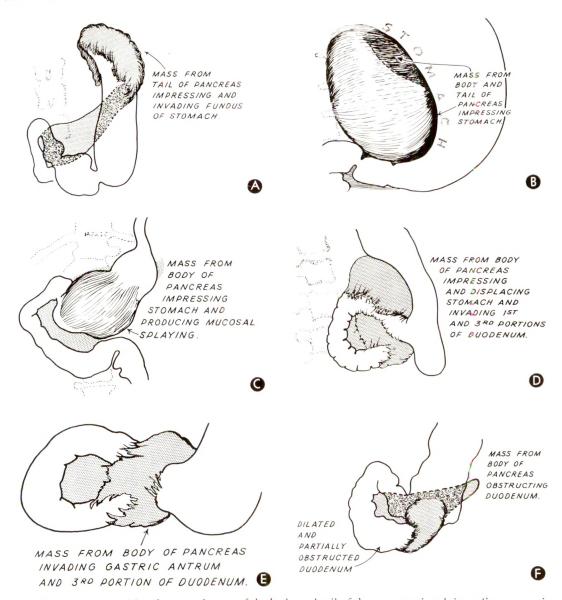


Fig. 2. Tumor masses arising from carcinoma of the body and tail of the pancreas involving adjacent portions of the stomach and duodenum. (A) Eccentric growth from the tail of the pancreas involving the gastric fundus. (B) Large mass impressing the lesser curvature. (C) Stomach draped over mass. (D) Note the characteristic retrogastric space widening by the tumor mass impressing and displacing the stomach anteriorly. (E) Roentgenograms would show an antral deformity not unlike a gastric carcinoma and a disrupted mucosal pattern of the invaded third portion of the duodenum. (F) Eccentric tumor growth involving only the junction of the third and fourth portions of the duodenum.

involved the body of the pancreas, which underlies the body and proximal antrum of the stomach, this figure was not surprising. In 2 patients, the fundus was anteriorly displaced. Significantly, the lesions in both were located in the tail of the pancreas.

Changes produced by extrinsic mass included either a distinct impression defect

(Fig. 2 B; and 4, A-F) or splaying of the gastric folds (Fig. 2 C; and 5, A and B). Of the 31 extrinsic masses demonstrated, all showed impressions and 6 further demonstrated splaying of folds. Again, most of the changes were noted in the gastric body. Of interest were 10 instances of impression of the gastric fundus. Of these, 3

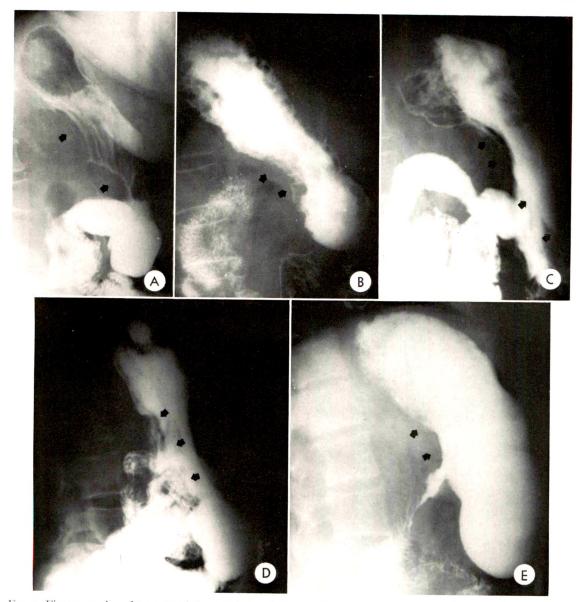


Fig. 3. Five examples of retrogastric impression and anterior displacement of stomach from carcinoma of the body and tail of the pancreas. (A, B and C) Arrows indicate gastric impression and displacement by tumor masses. (D) Irregular mass producing impression of posterior gastric wall (arrows). (E) Minimal impression of stomach by mass in body of pancreas (arrows).

resulted from lesions in the tail of the pancreas and showed only fundal defects. In 6 of the remaining 7, the tumor involved both the body and tail of the pancreas and the "impressed" area included the gastric body or antrum, or both.

Gastric invasion is indicated by one of three appearances: fixation of the gastric wall with intact mucosal folds (Fig. 6, A-F); fixation with mucosal destruction

(Fig. 2, A, D and E) or ulceration (Fig. 7, A and B), or both; and complete or incomplete gastric obstruction. In this series, 19 instances of gastric invasion were noted. In 10, fixation of the gastric wall with intact mucosa was seen, and in 9, fixation with mucosal destruction or ulceration. In none was there intraluminal extension or evidence of gastric obstruction.

Duodenum. For the purposes of this

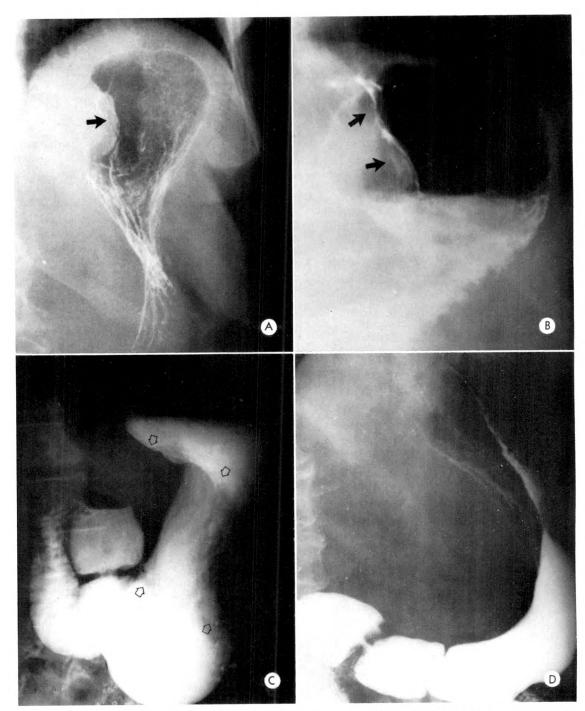


Fig. 4. Examples of extrinsic impression of stomach by carcinoma of body and tail of pancreas. (A and B) Impression of gastric cardia (arrows) from carcinomas of tail of pancreas. (C) Impression of body and fundus of stomach (arrows) by large mass located in body and tail of pancreas. Stomach is wrapped about mass, which protrudes anteriorly. (D) Huge mass in body and tail of pancreas impressing lesser gastric curvature.

study, the division of the duodenum into 4 parts was most useful. The first portion of the duodenum is defined as the bulb and the second as the descending duodenum. The third portion extends from the second





Fig. 4. (*E* and *F*) Impression of gastric antrum by mass in proximal body of pancreas (solid arrow) is from below. Note disturbed mucosal pattern of third and fourth portions of duodenum in *F*, indicating invasion (open arrows).





Fig. 5. Two examples of carcinoma of body of pancreas impressing stomach and producing splaying of mucosal folds. Note splayed mucosal pattern over dome of mass in both cases (arrows). (A) Carcinoma of proximal body of pancreas impressing gastric antrum. (B) Carcinoma of body of pancreas impressing body of stomach.

duodenum to the crossing of the superior mesenteric vessels where the bowel normally begins a slightly ascending course.







Fig. 6. Six examples of gastric invasion without ulceration from carcinoma of the body and tail of the pancreas. (A and B) Invasion of gastric fundus by carcinoma of tail of pancreas (arrows). Note that impression defect in fundus is also present. (C) Carcinoma in body and tail of pancreas producing impression, displacement, and invasion of body and cardia of stomach (open arrows). Note invasion of first portion of duodenum as well (solid arrows).

From the end of the third portion to the ligament of Treitz is defined as the fourth duodenum. The body of the pancreas is adjacent to a portion of the third duodenum and is partially covered by the fourth

duodenum. The ligament of Treitz approximates the junction of the body and tail.

Duodenal involvement was disclosed in 34 of the 46 patients studied. The categories of findings are the same as for the

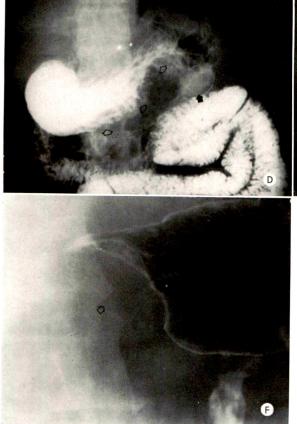




Fig. 6. (D) Carcinoma of body of pancreas impressing and invading greater curvature of stomach (open arrows). Solid arrow indicates barium in colon from prior study. (E) Invasion of lesser curvature of stomach from carcinoma of body of pancreas. Resultant slight filling defect and irregularity of wall simulates primary carcinoma of stomach. (F) Spot roentgenogram showing impression and invasion of distal, greater gastric curvature (arrow) by carcinoma of body of pancreas. Note mucosal irregularity.

stomach, *i.e.*, displacement, impression by extrinsic mass, and invasion (Table v). Duodenal displacement was noted 20 times, occurring almost exclusively in the third and fourth portions. Displacement was noted in all but the posterior direction. Several times it was in more than one direction.

An extrinsic mass was present in 23 patients of whom 19 had impression defects. All but 3 of these defects were in the third and fourth duodenum (Fig. 8, A-E). Splaying of mucosal folds was noted 12 times, all in the third and fourth duodenum. In 4 subjects, the only finding to substantiate a mass was splaying.

Signs of invasion were present in 28 patients and duodenal obstruction to some degree in 19. The area most commonly obstructed was the third portion of the duodenum at or just distal to its junction with the second duodenum (Fig. 2, D, E and F;

and 9, A–F). Such an obstruction was noted 12 times. In 6 other instances, the distal portion of the third duodenum was obstructed. One obstruction occurred in the fourth duodenum. Fixation of mucosal folds, which occurred 16 times, involved the third or fourth, or both, portions of the duodenum in all but 2 instances (Fig. 10, A–E). The 6 instances of ulceration or mucosal destruction all involved the third or fourth duodenum.

Colon. Barium enema examinations were performed on 24 patients (Table III), of whom 9 had changes in the distal transverse colon or in the splenic flexure, or in both. Of these, 5 tumors were in the tail of the pancreas and 4 in the body.

Displacement in the transverse colon was cephalad in 1 instance and caudad in 4. The splenic flexure was displaced downward in 1 patient.

Extrinsic mass caused impression on the



Fig. 7. Two examples of carcinoma of the body and tail of the pancreas producing gastric invasion and ulceration. (A) Gastric invasion from carcinoma of the body of the pancreas producing a large antral ulcer (arrow). (B) Large ulceration in posterior gastric wall (solid arrow) from invading carcinoma of tail of the pancreas. Barium flows through perforation of gastric wall into lesser sac (open arrow).

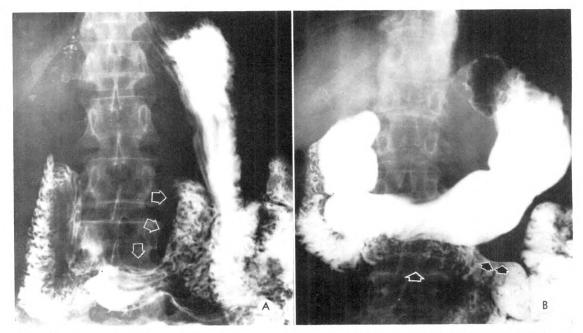


Fig. 8. Four examples of duodenal impression from carcinoma of the body and tail of the pancreas. (A) Fourth portion of duodenum is impressed from above (arrows) by tumor from the body of the pancreas. (B) Fourth portion of duodenum is impressed and splayed (open arrow) over a mass in the body of the pancreas. Note depression of the duodenojejunal junction by tumor (solid arrows).

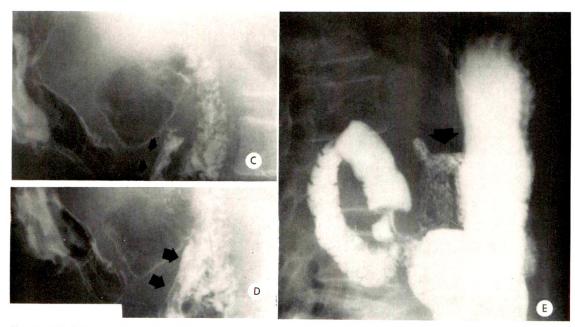
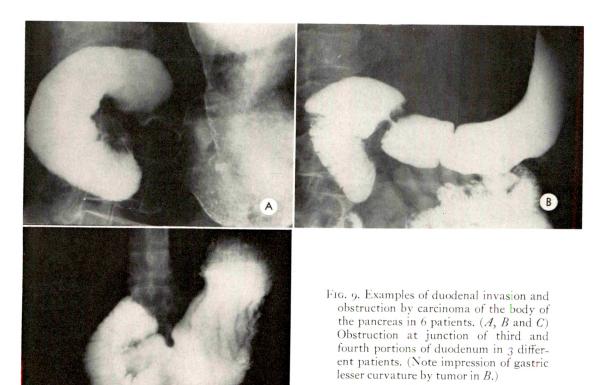
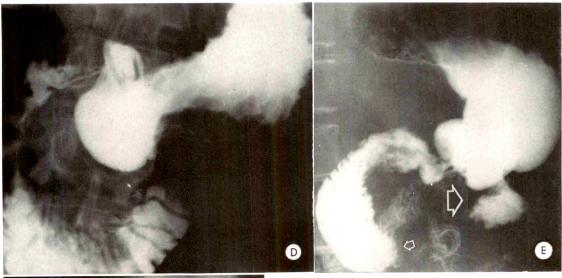


Fig. 8. (C) Mass in the body of the pancreas flattens the anterior border of fourth portion of duodenum. (D) Same patient. Slight oblique spot roentgenogram better demonstrates the impression. (E) Mass in the body of the pancreas impressing the duodenojejunal junction.





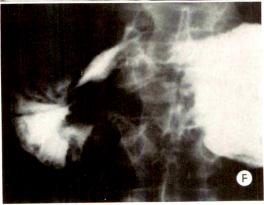


Fig. 9. (D) Obstruction in fourth portion of duodenum with mass impressing medial wall of duodenal sweep. (E) Obstruction at junction of third and fourth portions of duodenum (open arrow). Note anterior displacement of duodenojejunal junction (white arrow) by the large mass. (F) Obstruction in third portion of duodenum.

transverse colon 3 times and on the splenic flexure once. Splaying of the mucosal folds of the transverse colon was evident in 1 patient. Invasion of the splenic flexure was present in 2 instances and obstruction occurred once (Fig. 11, A and B).

OTHER ROENTGEN MANIFESTATIONS OF THE PRIMARY LESION

A soft tissue mass in the area of the pancreas was noted in 11 patients; in none was calcification present. Nothing except location was characteristic of the masses.

Occasionally, carcinoma of the body and tail of the pancreas extends into the ampullary region. This extension produces changes that on gastrointestinal examination are consistent with those of a primary lesion of the head.

The spleen was judged to be enlarged in 10 patients. No correlation existed between splenic enlargement and location of tumor as to body or tail. The location was evenly divided between neoplasms of the body and those of the tail. The cause of splenomegaly in these patients is usually attributed to obstruction of the splenic vein.¹⁹

McClellan²⁰ and Schorr and associates²⁴ noted the left kidney to be lower than the right in approximately 10 per cent of the normal population. In 10 of the 20 pyelograms of the present series (50 per cent), the left kidney was lower than the right.

MANIFESTATIONS OF METASTATIC LESIONS

Evidence of metastatic disease to the lungs was present in 3 patients. One in-

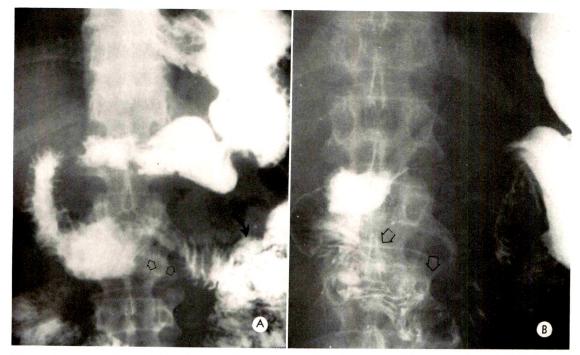


Fig. 10. Five examples of duodenal invasion by carcinoma of the body and tail of the pancreas. (A) Disturbed mucosal pattern of fourth portion of duodenum (open arrows) from invading carcinoma of body and tail of the pancreas. Curved arrow indicates depressed duodenojejunal junction by tumor. (B) Invading carcinoma of body of the pancreas distorts mucosa of third and fourth portions of duodenum.

stance of pulmonary infarction coincident with the discovery of the pancreatic neoplasm was documented. In 10 other patients, roentgen findings were compatible with pulmonary infarction during the course of the disease.

Oral cholecystography resulted in non-visualization of the gallbladder in 7 of the 12 patients undergoing such examinations.

Osseous abnormalities from carcinoma of the pancreas do occur, but uncommonly. No definite metastatic bone lesions were noted in this series. Two patients, however, manifested destruction of a lumbar vertebra from direct invasion.

Abdominal metastasis may appear as a rectal shelf lesion, *i.e.*, an indentation of the anterior rectum. A lateral view of the barium filled rectum best delineates this abnormality. In the present study, only one rectal shelf lesion was seen; however, the lateral view of the rectum was obtained in only 10 patients.

DISCUSSION

The above results indicate the variety of manifestations of carcinoma of the body and tail of the pancreas that are reflected in roentgenograms. To determine the presence of neoplasms in the body and tail of the pancreas, an upper gastrointestinal study is the most rewarding. Changes in the stomach were seen in 83 per cent and in the duodenum in 74 per cent. The signs to be sought primarily include those that give evidence of an extrinsic mass on the barium filled gut and of displacement or invasion. Similar but temporary alterations in the stomach and duodenum may also occur with normal peristalsis. Similarly, changes in the nature and volume of intraluminal content and various intra-abdominal pressures and positions may contribute to these alterations.

Changes produced by an extrinsic mass were divided according to findings of either a definite extrinsic deformity on the bowel

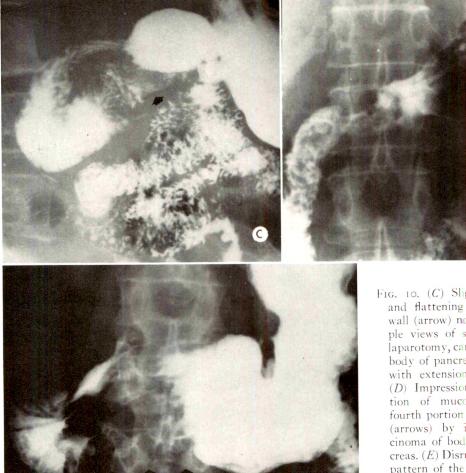


Fig. 10. (C) Slight stiffening and flattening of duodenal wall (arrow) noted in multiple views of same area. At laparotomy, carcinoma of the body of pancreas was found with extension to this site. (D) Impression and distortion of mucosal folds of fourth portion of duodenum (arrows) by invading carcinoma of body of the pancreas. (E) Disrupted mucosal pattern of the third portion of duodenum (arrows) from invasion of body of the pancreas.

or of splaying of the mucosal folds. Both findings, however, represent the same process. The appearance of splaying is noted only when the mass compressing the bowel is at an angle of 180° to the roentgenray beam. Splaying produces a characteristic appearance manifested by an involved segment that is wider than the adjacent uninvolved portions. The mucosal folds appear stretched and separated. This change was of great aid in detecting abnormalities of the stomach and of the third and fourth duodenum. It was frequently the most convincing evidence of a lesion in

an area of concern. Splaying may also be observed in the gastric antrum or in the third or fourth portions of the duodenum in normal patients. It is present only over that portion of the stomach or bowel that overlies the spine, whether the roentgenograms are obtained anteroposteriorly or posteroanteriorly.

The frequent presence of gastric findings emphasizes the need for an overhead, lateral view of the stomach with the right side dependent. This position permits the antrum and posterior wall of the lesser curvature to distend with barium and to

lie against the pancreas. This was the most rewarding view of the stomach in this series. It is essential in assessing anterior displacement of the stomach. In this view, an impression or anterior displacement by a retrogastric mass may be readily seen. Attempts at measuring the retrogastric space to detect anterior displacement when impression is lacking are unreliable. 14,25

Both gastric and duodenal changes were apparent in roentgenograms of 30 patients (65 per cent). These observations were possible in many instances because of the overhead right lateral recumbent view.

For a better study of the third and fourth duodenum, spot roentgenograms including the entire area during fluoroscopy are suggested. The second, third, and fourth portions of the duodenum should be distended with barium for this study. Exposures are obtained in two projections: the

 $T_{ABLE}\ V$ duodenal roentgen findings in 46 cases of carcinoma of body and tail of pancreas

Roentgen Findings	No. of Times Occurred	Description	
Displacement	20*	Right	5
	(43%)	Left	5 2 2
		Superior	2
		Inferior	IO
		Anterior	6
Invasion	28† (61%)	Fixation of wall with intact mucosa and /or edema	16
		Destruction of mu- cosa and/or ulceration	6
		Obstruction, partial or complete	19
Extr <mark>i</mark> nsic mass		Impression defect	19
	(50%)	"Splaying" of mucosal folds	I 2

^{*} In several instances displacement occurred in more than one

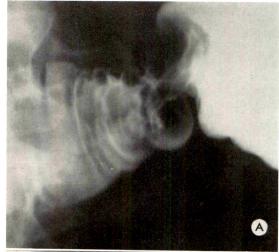




Fig. 11. Two examples of invasion of large bowel from carcinoma of body and tail of the pancreas. (A) Extension of carcinoma of body of pancreas to distal transverse colon simulating primary annular carcinoma of the colon. (B) Obstruction in splenic flexure during barium enema examination, simulating primary carcinoma of colon. Primary lesion was located in tail of pancreas.

supine left anterior oblique, which allows the duodenum to lie against the pancreas, and the prone right anterior oblique to ensure adequate filling of the loop.²²

No esophageal abnormalities were demonstrated in this series. Sloan and Wharton,²⁷ however, described changes in the distal esophagus, interpreted as cardiospasm, in a patient complaining of pro-

[†] Several patients had 2 or more types of invasion.

[‡] In 8 patients, combined impression and splaying occurred.

gressive dysphagia. Complete obstruction was present at esophagoscopy. At surgery, a carcinoma of the body and tail of the pancreas was found, which extended to the lower esophagus. Strang and Walton³⁰ reported 2 cases of dysphagia resulting from a tumor of the body and tail of the pancreas. The tumor extended to the esophageal hiatus and produced obstruction. In one of these, cardiospasm had been diagnosed roentgenologically. The proximity of the tail of the pancreas to the hiatus of the esophageal diaphragm was the explanation for this particular manifestation.

With isolated tail lesions, changes may also appear in the transverse colon, or in the splenic flexure.

The major changes of the colon to be looked for in carcinoma of the body and tail of the pancreas are as follows: (a) displacement of the distal transverse colon or of the splenic flexure, usually downward; (b) widening of the space between the greater gastric curvature and transverse colon;¹³ and (c) occasional invasion of the colon, sufficient at times to suggest an annular constricting primary carcinoma of the large bowel.³³

As the splenic vein courses along the upper edge of the pancreatic tail, it may be occluded by growing tumor. Should this occur, consequent splenic congestion and enlargement are frequently found. Splenomegaly was present in 10 of our subjects and in 5, complete obstruction of the splenic vein secondary to neoplasm was demonstrated at necropsy. When splenic vein obstruction occurs, varices of the gastric fundus may be detected either with or without esophageal varices. Gastric varices result from collateral circulation around the thrombosed splenic vein. Marks et al.19 reported a case of massive hematemesis resulting from ulceration of isolated varices of the gastric fundus. These varices were the result of obstruction of the splenic vein from a carcinoma of the tail of the pancreas. Several reports21,22 have stressed the importance of splenoportography in suspected carcinoma of the pancreas as a means of demonstrating splenic or portal vein invasion.

The 50 per cent incidence of a left kidney that is lower in position than the right is 5 times greater than normally expected. This difference alone cannot be considered important for the diagnosis of pancreatic neoplasms as it occurs frequently in the general population. If it is associated with more reliable signs, however, it lends support to the diagnosis.

A relationship between carcinoma of the pancreas and venous thrombo-embolic phenomena was stressed in 1865 by Trousseau, as cited by Sproul.²⁹ Gullick¹² reported both arterial and venous thrombo-embolic activity in carcinomas of the body and tail of pancreas in 50 per cent of the patients. He stated that pulmonary emboli alone occur in 8.3 per cent. Strang and Walton³⁰ stated that the number of thrombo-emboli in carcinoma of the body and tail was twice that of carcinoma of the head (50 per cent versus 25 per cent). The suspicion that pulmonary infarcts are present in a given case is of little help because pulmonary infarction per se is so frequent. When roentgen findings suggest pancreatic neoplasm, chest findings compatible with pulmonary infarction further support this impression.

Nonvisualization of the gallbladder was noted on roentgenograms of 58 per cent of the patients of this series undergoing oral cholecystography. This number is in contrast to the almost universal nonvisualization of the gallbladder in carcinoma of the pancreas limited to the head. Such nonvisualization in the latter is to be expected because of the peri-ampullary location of the primary lesions. In carcinomas of the tail and body of the pancreas, it is a reflection of metastasis to liver or to lymph nodes of the porta hepatis.5 Direct extension of the neoplasm into the head, producing ampullary obstruction, also results in nonvisualization. Visualization of the gallbladder does occur in approximately 50 per cent of the patients with carcinomas of the tail and body of the pancreas. This finding should not be interpreted as mitigating against the diagnosis of pancreatic carcinoma.

The extremely high degree of accuracy of delineating abnormalities secondary to these neoplasms must be understood in light of the pathogenesis of this disease. In all cases the disease is far advanced by the time the patient has symptoms. Gullick¹² reported that metastatic growth produced the initial symptoms in 21.7 per cent of the patients with lesions of the body and tail of the pancreas. The advanced state of the disease, therefore, facilitates diagnosis. The size of the primary lesion or of its associated metastatic deposits is, at this time, sufficient to cause intra-abdominal abnormalities. These can be discerned when the diverse manifestations of the disease are known. The invariable incurability at the time of initial examination should not discourage an attempt at diagnosis.

Several of the changes described for carcinoma of the body and tail of the pancreas may be seen in other diseases. The differential diagnosis must include pancreatitis, pancreatitis with pseudocyst formation, aortic aneurysm, lymphomas, and metastatic carcinoma to retroperitoneal lymph nodes. Reliance on clinical, laboratory, and roentgen information often resolves the question of entity.

SUMMARY

Carcinoma of the body and tail accounts for 25 per cent of pancreatic neoplasms. Early symptoms are rare owing to the anatomic location. Metastasis often produces the initial symptoms. When body and tail carcinoma is suspected, a lateral view of the stomach and spot roentgenograms of the third and fourth duodenum are essential. The areas most frequently affected are the body of the stomach and the third and fourth duodenum. Anatomically, these areas are in closest relationship to the body of the pancreas, which is involved in 85 per cent of all body and tail neoplasms.

The distal esophagus, gastric fundus, transverse colon, and splenic flexure may be involved, particularly in lesions confined to the tail of the pancreas. Noteworthy findings to be observed on plain roentgenograms include a soft tissue mass in the region of the pancreas and an enlarged spleen.

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CARCINOMA OF THE PANCREAS

A BI-DIRECTIONAL ROENTGEN APPROACH

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BARIUM studies have remained the key to roentgen diagnosis of carcinoma of the pancreas in spite of recent development of other procedures. Numerous difficulties in diagnosis beset the radiologist, even when he is alerted to the problem by the clinician, not to mention the silent elusive lesion. Some groups rate the percentage accuracy of preoperative roentgen diagnosis as low as 30 per cent, whereas others claim 75 per cent accuracy in lesions of the head of the pancreas. Numerous signs have been presented in the past by many investigators, each one with certain limitations.

The purpose of the author is to unify these various parameters in a concept of bidirectional approach to this difficult problem. The various roentgen criteria may be roughly subdivided into two major categories; namely, a geometric concept and a morphologic concept. When roentgen criteria are present in only one category, a reexamination is indicated in an attempt to demonstrate manifestations in the other category. If after the second examination the positive signs are still present in one category, the percentage accuracy of preoperative diagnosis drops significantly. It is in these cases that other modalities play a noteworthy and determining role. Selective celiac angiography with or without associated superior mesenteric angiography is most important in this connection. This bidirectional approach has improved our diagnostic acumen in many elusive cases.

1. THE GEOMETRIC CONCEPT

The geometric approach has had many proponents since it was introduced by Engel and Lysholm,⁷ in 1934. Poppel^{19,20}

advocated the supine translateral exposure for lesions of the body of the pancreas (Fig. 1, A and B). Sheinmel and Mednick²⁶ in 1951 tabulated retrogastric measurements in normal patients of different habitus, in an attempt to standardize the upper abdomen. Even though one recognizes the vitiating effects of obesity and ascites, any familiarity with the subject will indicate that such major normal variations exist to cast doubt on the whole procedure. It may be very enticing to emulate the geometric approach to intracranial masses, but a fixed cranium and a semi-elastic mobile abdomen are not truly comparable. Too many variables exist, the most obvious being habitus, state of tone of various structures (especially the musculature of the abdominal wall), ascites, obesity, etc. Furthermore, several planes exist in the abdomen: (a) the spine and posterior abdominal wall, the retroperitoneal plane (genitourinary, pancreatic, etc.), (c) the gastrointestinal plane, and (d) the anterior abdominal wall (Fig. 2). It is, therefore, easy to understand why many radiologists have lost faith in the efficacy of this modality.

However, if one is prepared not to accept this "all or none" criticism, the results may be quite rewarding. Instead of a rigid approach to the retrogastric and retroduodenal space, a realistic flexible attitude should be adopted. Knowledge of the individual variations of this space due to habitus is invaluable as a broad generalization. In 1958, Beranbaum and Jacobson² advocated that enlargement of this space is not sufficient for a diagnosis of a mass, but must be combined with the associated displacement phenomenon, regardless how slight, utilizing the force of gravity to bring

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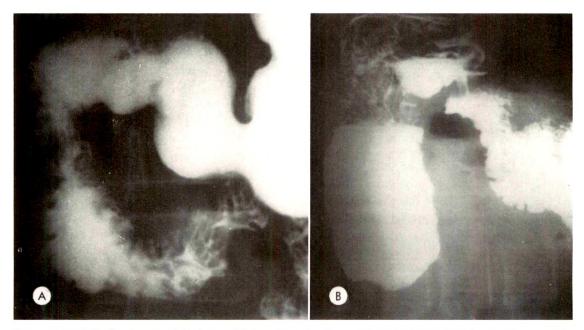


Fig. 1. (A and B) Carcinoma of the body of the pancreas in a hypersthenic individual, with extension into the uncinate process. In the supine translateral exposure (B), the stomach has been rotated so that its axis is perpendicular to the axis of the spine. The mid-line retrogastric space is increased and there is an extrinsic indentation defect on the inferior posterior aspect of the stomach. The main mass is in the body of the pancreas. The frontal exposure (A) presents thickened divergent folds in the third portion of the duodenum, indicating extension into the uncinate process.

out pressure indentation, shelving, etc.

Herbert and Margulis¹² have recently corroborated this contention in their statistical evaluation of retroperitoneal masses. They state, "Measurements alone were of little value in detecting an individual retrogastric or retroduodenal tumor but some combination might be helpful." Later, they continue, "Extensive tumor impression on the viscera was selected as the single most important statistical factor in evaluating the presence of a retroperitoneal mass."

More recently, a further modification has been made. Fundamentally, each patient is his own standard for his particular retrogastric space (Fig. 3, A and B; 14B; and 17B). Although this may seem elementary, slight deviations in the size of this space in the course of smoothly contoured organs (such as the descending duodenum) may be most significant even though "no enlargement" be present utilizing the usual criteria, In Figure 3 B, a right lateral study, there is no enlargement of the retroduo-

denal space, but if one were to extrapolate the proximal descending duodenum, the distal descending duodenum would be anterior to the actual location. Likewise, if one were to extrapolate the distal descending duodeum proximally, it would be posterior to its actual location. Admittedly, this finding by itself is quite meager, but accompanied by a morphologic defect (Fig. 3A) and a history of obstructive jaundice, a correct preoperative diagnosis was rendered. In other words, it is our contention that the retrogastric and retroduodenal space approach is most valid, but an individualization and flexibility to the problem must be present, combined with a common sense appraisal.

To date we have not modified our technique significantly. Routinely, 6 exposures of the opacified stomach and duodenum are made as follows:

(1) Posteroanterior upright for an evaluation of the (2) Left lateral upright space on the left

Fig. 2. Carcinoma of the tail of the pancreas. A left lateral exposure during intravenous pyelography demonstrates a mass indenting the gas filled cardia and pars media. There is minimal downward displacement of the kidney. The mass must, therefore, be between the genitourinary and gastrointestinal tracts and, of necessity, tail of the pancreas.



(3) Anteroposterior supine

(4) Supine translateral

as advocated by Poppel²⁰ for mid-line masses

(5) Prone

(6) Right lateral recumbent

for an evaluation of the space on the right side

On occasion, when indicated, supplementary decubitus or Trendelenburg position roentgenograms are also made to help gravity approximate the barium filled viscus to the mass in order to demonstrate the pad effect (Fig. 4).

Another source of error in evaluating the retrogastric space is due to the wrap around



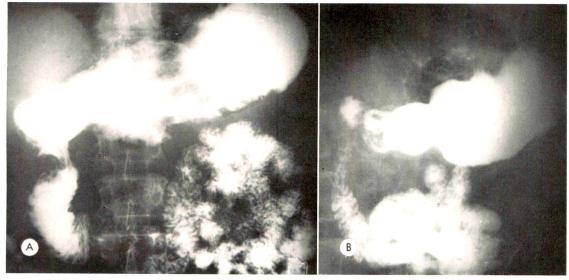


Fig. 3. (A and B) Supine and right lateral roentgenograms. Carcinoma of head of the pancreas. A gastro-intestinal series performed on a patient with obstructive jaundice was entirely negative excepting for the supine and right lateral roentgenograms. A nodular defect is noted on the convex side of the descending duodenum, with an inverted 3 sign on the concave side. In the supine position, the pancreas indents the adjacent duodenum to elicit early pressure defects. In the lateral view, there is no enlargement of the retroduodenal space, but differential size in the space is present.



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Fig. 4. Pad sign in carcinoma of the body of the pancreas. Compare with Figures 8, *A*–*D* and 9, *A* and *B* which illustrate the pad sign of carcinoma of the tail of the pancreas.

effect of the heavy barium surrounding the mass. The mass indents and displaces that portion of the posterior wall of the stomach immediately in contact with the mass. With overfilling of the stomach with barium, the posterior wall on either side of the mass is not displaced. In a well penetrated lateral roentgenogram, that portion immediately in contact with the mass must be carefully differentiated from the remainder of the posterior wall of the stomach (Fig. 5).

Figure 6, A and B illustrates the same point in a different manner. Two left lateral upright roentgenograms were taken about 30 minutes apart because of motion. With the stomach full, there is no apparent enlargement of the retrogastric space. With gradual emptying of the stomach, there is evidence of a large retrogastric space. Indeed, pneumography, as advocated by Engel and Lysholm,7 has certain advantages over barium in this regard. In I patient a diagnosis of a retrogastric mass (later proven to be tail of pancreas) was made on the basis of anterior displacement of a large gas bubble of the stomach observed in a routine lateral exposure of the chest.

The supine translateral exposure advocated by Poppel²⁰ is not universally employed in cases of suspected pancreatic disease. We have cases on record in which

this presented the only clue to a diagnosis of a lesion of the body. Besides enlargement of the retrogastric space, a rotational effect of the mass may be observed. The mass rotates the stomach along its organic axis, in the supine translateral position, so that in the hypersthenic patient, the axis of the stomach is perpendicular to the axis of the spine (Fig. 1B). Since evaluation of enlargement of the retrogastric space is most difficult in hypersthenic patients, an appreciation of this right angle rotational sign should alert the examiner to attempt additional studies to demonstrate a pad defect (for instance, a Trendelenburg position study—Fig. 4), if no shelving or pressure defect is present in the routine supine translateral roentgenogram. The rotational effect may at times be more pronounced and result in a partial organo-axial volvulus. Therefore, a mass in the lesion of the body of pancreas should be thoroughly investigated in patients with apparent "idiopathic" organo-axial volvulus. This has been described in 1954 in an evaluation of

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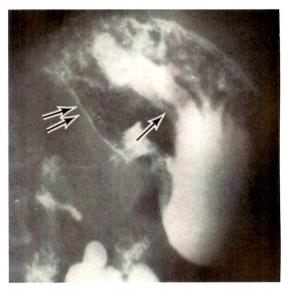


Fig. 5. Carcinoma of the entire pancreas. Note the displacement and distortion of the diverticulum, the postbulbar narrowing, and the enlarged retrogastric space. The wrap-around effect is illustrated with the single arrow pointing to the posterior wall of the stomach in contact with the mass. The double arrow indicates the posterior wall of the stomach lateral to the mass.

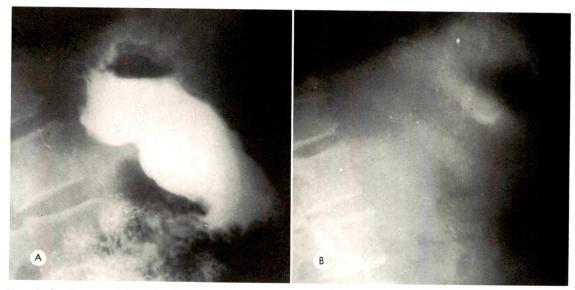


Fig. 6. Carcinoma of the tail of the pancreas. (A) Left lateral roentgenogram shows no retrogastric space enlargement. (B) Thirty minutes later, with the stomach empty, the retrogastric space is markedly enlarged. Barium, due to wrap-around effect, may obscure large tumors. The importance of a detailed evaluation of gas shadows is demonstrated.

gastric volvulus. The rotational effect also uncovers the angle of Treitz, thereby rendering a better appreciation of loop enlargement (Fig. 7 and 29).

The right lateral study is probably the easiest to evaluate, since the numerous morphologic signs about the duodenal sweep enable a more definitive statement. Nevertheless, it must be recalled that an enlarged right retrogastric and retroduodenal space may indicate a mass in any one of the retroperitoneal structures, not necessarily pancreatic, Although a pancreatic carcinoma usually displaces the descending duodenum anteriorly, a mass attached to the anterior wall only may displace the duodenum posteriorly producing a decrease of the retroduodenal space (Fig. 10; 11, A and B; and 12, A, B and C). An increase in the retroduodenal space proximally, but not distally, associated with a relatively sharp change in direction may be most significant of a localized mass (Fig. 3, A and B).

The left retrogastric space requires a more critical evaluation. The tone of the anterior abdominal musculature is a determing factor in the upright study. For this



Fig. 7. Carcinoma of the head of the pancreas. A large common bile duct produces an indentation on the superior aspect of the postbulbar duodenum and a double contour on the concave aspect of the descending duodenum. Compression studies often help to delineate the double contour. The stomach is partially rotated along its organic axis, thereby uncovering the angle of Treitz which is partially depressed. Loop enlargement is, therefore, better appreciated.

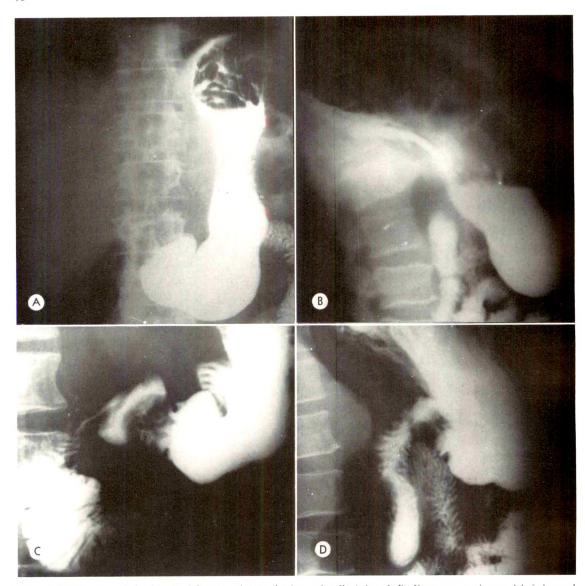
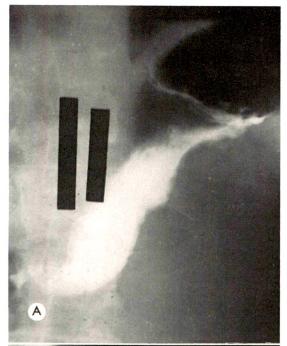


Fig. 8. Carcinoma of the head with extension to body and tail. (A and B) Posteroanterior and left lateral upright roentgenograms. Note characteristic location and type of indentation due to the tail. It is just below the fundus on the lesser curvature, and indents the posterior wall at the same level. (C) Note bulbar defect with ulceration, postbulbar narrowing with distal distention with ledge formation due to the mass, partial obstruction at 3rd portion of the duodenum with irregularity of mucosa with erosions at the 3rd portion of the duodenum. (D) Right lateral recumbent roentgenogram. The enlargement of the retrogastric space is debatable due to the wrap-around effect. Fortuitously, the mass indents the gas filled colon. The descending duodenum is displaced anteriorly, especially inferiorly. The superior portion of the descending duodenum presents a widening and separation of the folds with picket fence formation.

reason, in patients with flabby musculature, a left lateral recumbent roentgenogram may be much more revealing. Indentations on the posterior wall of the stomach do not necessarily implicate the tail of the pancreas. Starting cephalad, an indentation

high up is usually due to the left lobe of the liver, spleen, or any other mass in the left subphrenic region. Characteristically, an indentation due to the tail of the pancreas is located just below this level and does not extend up to the level of the diaphragm



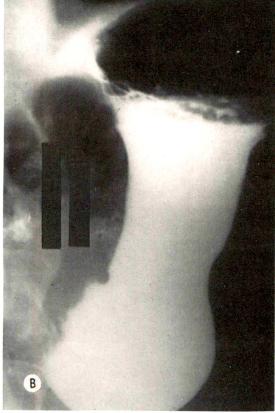


Fig. 9. (A and B) Carcinoma of the tail of the pancreas. The lesion was not detected on the initial examination and was discovered 6 months

(Fig. 8, A - D; and 9, A and B), except when the lesion is much larger and more readily demonstrated. An error in the opposite direction may occur by misinterpreting an indentation below this level due to a normal or large kidney as a mass in the tail of the pancreas. A large left kidney and, at times, even a normal left kidney may indent the posterior wall of the stomach, especially in the upright posture if it rotates along its longitudinal axis.

Anterior displacement of the duodenojejunal junction may occur due to masses in this location. Since a certain degree of variability in the peritoneal reflections exists in this region, this sign is not specific for pancreas. Displacement may be noted not only with masses of the pancreas but with any other retroperitoneal masses. Furthermore, we have observed a patient with a mesenteric cyst with considerable anterior displacement of the duodenojejunal junction.

The possibility of false positives must be always considered before rendering an opinion. An awareness of this pitfall should stimulate the examiner to obtain additional evidence. In a recent article, Schultz²⁵ has outlined the sources of errors (obesity, previous surgery, hernias involving the omentum, gross hepatomegaly, ascites, or emphysema).

Cinefluorography alone without benefit of large conventional roentgenograms cannot visualize adequately the retrogastric

later. Retrospectively, the only roentgenograms that presented a clue were the two spot roentgenograms illustrated. A left lateral upright exposure was not made initially. In A, the mass displaces the stomach medially. In B, with complete filling of the stomach, the medial displacement is no longer evident, but the pad effect is noted on the lesser curvature of pars media. A study of the upright abdominal roentgenogram without contrast medium is, at times, superior to the barium study in delineating this pad effect. The swinging of the stomach laterally and medially is an indication that the stomach has not yet been fixed in position by the tumor. It is seen more readily with cysts than with carcinoma.

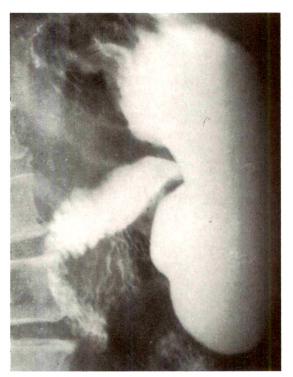


FIG. 10. Carcinoma of the head of the pancreas. A small tumor, 2 cm. in diameter. No enlargement of the retroduodenal space, but there is posterior displacement of the descending duodenum. A mass is evident with slight distortion and widening of the folds of the descending duodenum. A linear brush stroke appearance of the folds in 3rd portion is purely a pressure phenomenon. Location of the tumor is more important than its size for its early detection.

space, and, therefore, robs itself of an important method in detecting elusive pancreatic or other retroperitoneal masses.

In summation, the retrogastric and retroduodenal space must be evaluated critically and individually. Sweeping generalizations will lead to erroneous conclusions. Common sense specifically oriented towards this entity will aid considerably.

THE MORPHOLOGIC CONCEPT

The morphologic changes of the barium filled duodenum and adjacent stomach and jejunum are dependent on the intimate association primarily of the head of the pancreas to these structures. The descending duodenum, in particular, is vul-

nerable to changes in view of its retroperitoneal location. An evaluation of the various signs of pancreatic malignancy will be undertaken with emphasis on their significance, especially with reference to the differentiation from benign disease (primarily pancreatitis).

I. ENLARGEMENT OF THE DUODENAL SWEEP

This sign is considered to be the *sine qua* non by most clinicians, although in its usual connotation it is probably the poorest sign of malignancy. Enlargement of the sweep is readily visible in benign disease, especially in cystic disease. Enlargement of the sweep in malignant disease is indicative of most advanced disease. Nevertheless, the concept of an enlarging mass producing local displacement effects is valid. The sweep may not be, and most often is not, enlarged per se (Fig. 10), but slight stretching effects, especially on the mucosal folds, may be most significant in producing a pad type of defect enunciated by Case.4 This enlargement of the sweep may not be readily discernible when one looks purely at the duodenum. The two ends of the sweep are the tell-tale indications of a mass which produces a general displacement pad defect (Fig. 7). The greater curvature of the antrum presents an oblique pressure cutoff. This is often mistaken as spine pressure since in the prone position roentgenogram it overlies the spine. More critical evaluation will indicate that the greater curvature just proximal to this obliquity is also over the spine and not involved. Likewise, the 3rd and 4th portions of the duodenum, including the duodenojejunal junction may be stretched and/or depressed (Fig. 7 and 29) with or without change in configuration. The entire area from antrum to angle of Treitz must be considered as one entity from the point of view of enlargement, rather than a simple mistatement of the "duodenal sweep." Unusual duodenal displacements may be present, but if the mass is always within the loop, the mass must be pancreatic (Fig. 12, A, B and C)

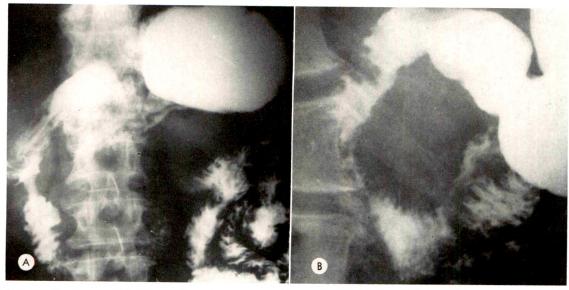


Fig. 11. Carcinoma of the head of the pancreas. (A) Supine study. This was superior than the prone study in depicting duodenal abnormalities. Note the narrowing in the proximal descending duodenum with rigidity and invasion. Distally the folds are widened, divergent and rigid. (B) Right lateral recumbent study. The retroduodenal space is decreased by the tumor. The slight asymmetric deviation is important diagnostically. The mucosal abnormalities are confirmed. Note nodular defect on posterior wall of the proximal descending duodenum (wrap-around effect).

2. PANCREATIC ULCER SIGNS

(a) Bulbar and Postbulbar Defects (Fig. 8C; 13; 14B; 15; 16, A and B; and 17, A and B). A malignant lesion of the pancreas locally invades and destroys adjacent tissues. The bulb is far from immune and, indeed, multiple bulbar defects with irregular irritability and intolerance for the barium may be pronounced, even with evidence of a crater. Too often a diagnosis of duodenal ulcer has been rendered, only later to reveal its true character. Recent onset of diabetes, plus a "duodenal ulcer" present roentgenographically a suspicious set of circumstances, meriting more detailed study.

(b) Postbulbar Narrowing (Fig. 5; 8C; and 25, A and B). Postbulbar narrowing most frequently is due to postbulbar ulcer. Nevertheless, it is also a sign of pancreatic malignancy. Differentiation from annular pancreas is evident by the mucosal destruction. Furthermore, the narrowing, in contradistinction to postbulbar ulcer narrowing, gives the impression of an associ-

ated mass, even when the edges are not truly overhanging. Furthermore, the superior portion of the narrowed segment is produced by the dilated common duct, whereas the inferior portion is produced by the pancreatic mass with local invasion. Differentiation from postbulbar ulcer is usually made readily.

3. MUCOSAL CHANGES

These have been admirably presented by Salik,²⁴ and merit re-emphasis with special comment (Fig. 1, A and B; 18; 19; 20, A and B; and 21, A and B). The folds on the inner aspect of the duodenum may present changes in shape, width, height and direction. A brush-like configuration, instead of the normal feathery appearance, is a sign of mass pressure with ironing out of the folds (Fig. 10). It does not differentiate between benign or malignant disease. Likewise, minor indentations or flattening of the medial ends of the folds may make the contiguous folds appear as a continuous concave line, rendering another manifesta-

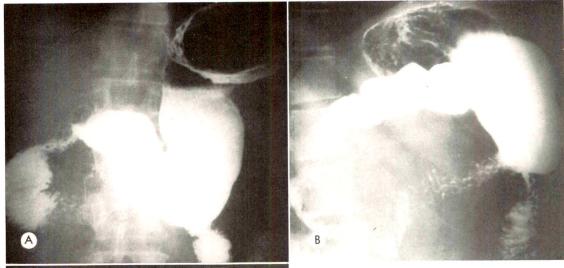




Fig. 12. (A, B and C) Cystadenocarcinoma of the head of the pancreas. This case has several unusual features. The descending duodenum is displaced laterally, rather than medially. The retrogastric space is enlarged, but the retroduodenal space is narrowed with the descending duodenum displaced posteriorly to a marked degree. The stomach is rotated on its organic axis so that it is perpendicular to the axis of the spine. Two fluid levels of an organo-axial volvulus are present. Yet, the descending duodenum is displaced superiorly so that it approximates the stomach rather than being separated from it (compare with Fig. 1, A and B). The one outstanding feature that makes this mass pancreatic, is the fact that the sweep is enlarged and in all exposures the mass is within the sweep.

tion of a mass, either benign or malignant. A markedly irritable descending duodenum produces a fleeting appearance in a thread like fashion with irregular skeletonization (Fig. 27). These findings do not differentiate carcinoma from pancreatitis.

From a practical point of view, the differentiation of carcinoma from pancreatitis is most vexatious from barium studies alone. To a considerable extent, this differentiation will depend on an evaluation of the mucosal changes. The changes outlined above are nonspecific in this regard and merely indicate the presence of a mass. Wide edematous folds, but no destruction, are more in favor of inflammatory disease.

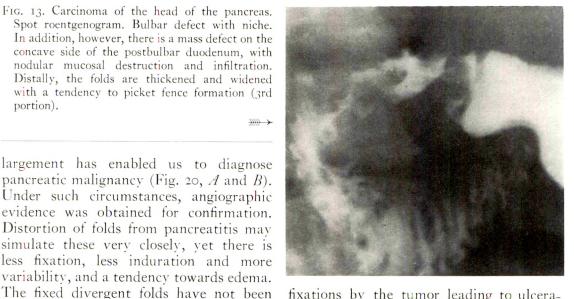
A spike-like configuration, or a picket fence configuration may be present in either case. However, when this becomes more pronounced and presents divergent thick folds with fixation, rigidity and induration, carcinoma must be suspected. The divergence of the folds is a manifestation of tumor spreading the folds apart after it has invaded the outer wall but not actually the mucosa. This divergence of the folds may be accompanied by marked fixation and spreading apart of the folds at their base, producing a corrugated appearance, which is more in favor of carcinoma than pancreatitis. Indeed, this sign alone without retrogastric or retroduodenal space en-

Fig. 13. Carcinoma of the head of the pancreas. Spot roentgenogram. Bulbar defect with niche. In addition, however, there is a mass defect on the concave side of the postbulbar duodenum, with nodular mucosal destruction and infiltration. Distally, the folds are thickened and widened with a tendency to picket fence formation (3rd portion).

largement has enabled us to diagnose pancreatic malignancy (Fig. 20, A and B). Under such circumstances, angiographic evidence was obtained for confirmation. Distortion of folds from pancreatitis may simulate these very closely, yet there is less fixation, less induration and more variability, and a tendency towards edema.

Elongation of folds with pseudodiverticulum formation is probably produced by

observed in pancreatitis.



fixations by the tumor leading to ulceration.

Mucosal destruction of various sorts may be produced by carcinoma, and enable

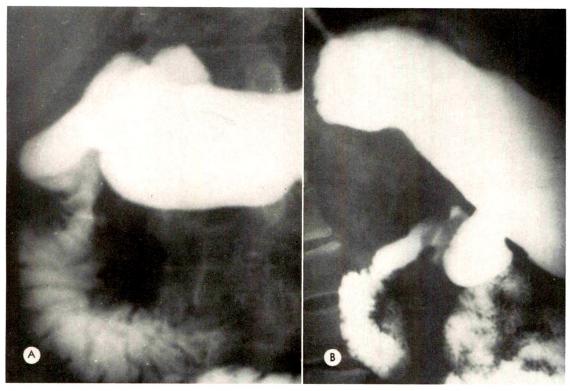


Fig. 14. (A and B) Carcinoma of the head of the pancreas. The frontal roentgenogram shows no abnormality on the concave side of the descending duodenum, but there is a nodular defect on the convex side with fixation and divergent separation of the folds. The lateral roentgenogram presents enlargement of the retrogastric and retroduodenal space. (Note differential displacement of descending duodenum.) Bulbar defect with ulceration is present.



Fig. 15. Carcinoma of the entire pancreas. Left lateral upright study. Enlargement of the retrogastric, but not the retroduodenal space. An indenture at this level is characteristic of a mass in the tail and body. The mass in the head is confined to the anterior aspect of the duodenum, producing nodular indentations with ulceration.

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a definite differentiation from pancreatitis. Proximally, this manifests itself as bulbar and postbulbar defects. In the descending duodenum, small nodular filling defects of varying degrees project themselves into the lumen (Fig. 19). The majority are eccentric and invade the medial border of the descending duodenum. The corrugated sign represents that stage of the disease just short of mucosal destruction with nodular intrusion.

The significance of the divergent fixed fold is well illustrated in Figures 1, A and B; 21, A and B; and 22, A and B. In these patients the malignancy involved the tail and body and extended towards the head.

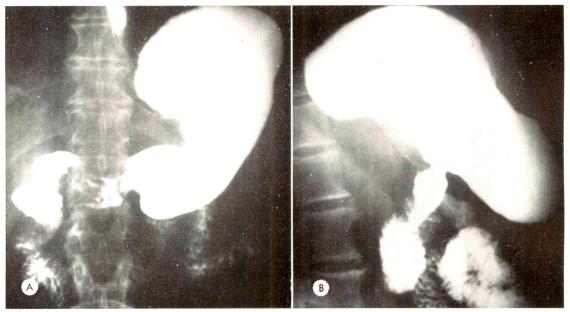


Fig. 16. Carcinoma of the head and body of the pancreas. (A) Defect is present on lateral aspect of descending duodenum with a huge ulceration. Antral deformity with mucosal distortion is also present. (B) Enlargement of the retrogastric and retroduodenal space. (Note differential enlargement of retroduodenal space.) The huge ulceration is again evident.

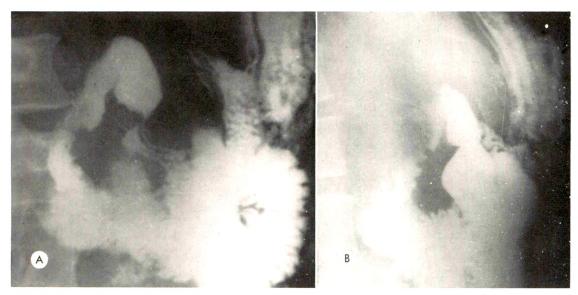


Fig. 17. Carcinoma of head and body of the pancreas. (A) Oblique roentgenogram with a large ulceration on the anterior wall of the descending duodenum. The proximal portion of the descending duodenum is deviated anteriorly. (B) The lateral roentgenogram demonstrates the anterior deviation to better advantage. The tumor is mainly posterior to the duodenum, with no enlargement of the loop. Only a portion of the descending duodenum is displaced. Differential displacement such as this is an important diagnostic feature.

In the area of extension, these mucosal changes are noted prior to the later stages of mass invasion. A study of the margin of the tumor affords an excellent opportunity

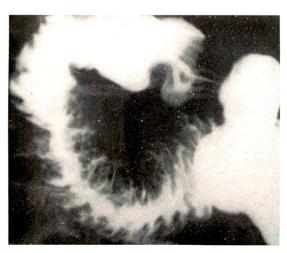


Fig. 18. Carcinoma of the head of the pancreas. No enlargement of the loop. Double contour (due to dilated common bile duct), and fold changes. The folds are thickened, rigid, fixed and, most important, divergent with the impression of a mass most evident at the junction of the 2nd and 3rd portions of the duodenum.

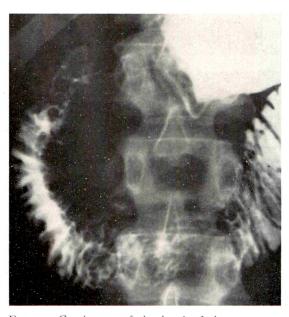


Fig. 19. Carcinoma of the head of the pancreas. The loop is stretched, but much more significant are the mucosal changes—elongation and stretching of the folds, widening of the spaces between the folds extending to small nodular impressions, small fistula formation (junction of 2nd and 3rd portions), rigidity and fixation. The indentation on the greater curvature of the antrum is due to the tumor and not the spine.





Fig. 20. (A and B) Carcinoma of the head of the pancreas in a patient with minimal complaints and no jaundice. Oblique studies in rapid sequence. The folds of the descending duodenum are indurated, thickened, spread apart and divergent. The folds of the 3rd portion of the duodenum are ironed out, irregular, and partially destroyed. Note differential anterior displacement of distal descending duodenum. The retrogastric and retroduodenal spaces in the lateral projection were normal. The possibility of pancreatic carcinoma was suspected. Celiac angiography was recommended in view of the minimal findings. Celiac angiography confirmed the diagonsis, which was proven surgically.

to evaluate the earliest mucosal changes produced by pancreatic carcinoma.

A nodular type of defect surrounded by barium may be present and simulate an actual intraluminal type of polypoid lesion (Fig. 23A). Careful rotation of the patient will indicate its extraluminal (Fig. 24) rather than its intraluminal character. The wrap-around effect may produce similar findings, simulating an intraluminal lesion (Fig. 25, A and B).

4. INVERTED 3 SIGN

The inverted 3 sign of Frostberg¹⁰ (Fig. 26) has been amply elucidated in the literature. It is an indication of a pancreatic mass, but does not differentiate carcinoma





Fig. 21. Carcinoma of the tail and body with slight extension to the head. (A) The lateral study indicates an increase in the retrogastric space with indentation on the posterior wall of the stomach. (B) Detailed study of the duodenum shows the thickened, indurated, fixed divergent folds at the duodenojejunal junction, indicative of invasion by the tumor. Brush stroke arrangement of the folds in the descending duodenum is merely an expression of an adjacent mass.

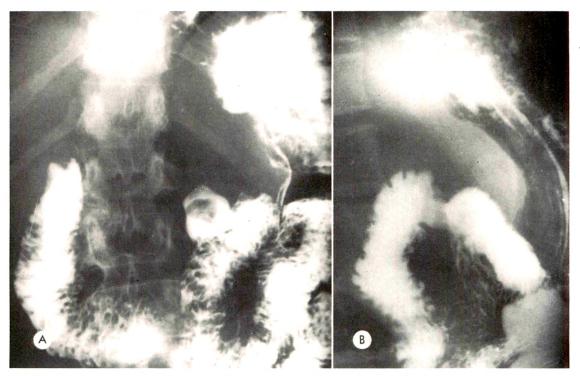


Fig. 22. Carcinoma of the body and tail of the pancreas with extension into the uncinate process. (A) Supine roentgenogram. A small nodular type defect is present at the junction of the 2nd and 3rd portion of the duodenum in the region of the uncinate process. The folds are distorted and irregular. A ring shaped calcification just above the duodenum represents a hepatic artery aneurysm. It could easily be mistaken for a gallstone. The defect was not well documented in the prone roentgenogram. The supine study in some cases may be the better for delineating the tumor when it extends posteriorly (see B). (B) The retrogastric space is enlarged with an indentation characteristic of the body of the pancreas. Note the anterior deviation of the distal descending duodenum even though the retroduodenal space is not enlarged. In addition, the thickened rigid divergent folds in the region of the uncinate process are prominent. The postbulbar indentation is due to a dilated common duct.

from pancreatitis. Associated mucosal distortion and/or destruction signs must be elicited in an attempt at differentiation.

5. DUODENAL DIVERTICULUM

A duodenal diverticulum acts as a probe into the pancreatic head. If fortuitously a lesion should start in this vicinity, it may be readily diagnosed at an early stage by displacement or compression manifestations (Fig. 5 and 28).

6. FIXATION AND WRAP AROUND EFFECTS

Fixation and wrap around effects may be noted by lack of mobility, rigidity and partial compression of the lateral aspect of the descending duodenum. Medial displace-

ment of the distal descending duodenum in the prone position is probably due to wrap around effect, with medial displacement accompanied by rigidity of the duodenum as it is attached to the tumor. In the literature defects on the concave side of the descending duodenum are repeatedly emphasized. But with the spread of the tumor in a wrap around fashion, similar defects may exist on all walls of the duodenum, including the convex lateral margin. The supine roentgenogram (Fig. 3, A and B; 11A; and 22A) is valuable in this regard, since barium pressing on the mass may present defects, not otherwise detectable. This study has not been emphasized in the literature, and is preferred to the left



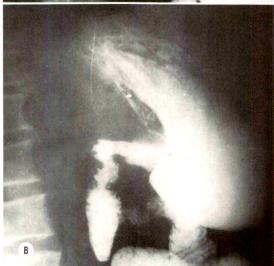


Fig. 23. (A and B) Carcinoma of head of the pancreas with extension to body. Note enlargement of retrogastric and retroduodenal space, bulbar deformity, irregular nodular invasion into proximal descending duodenum with ulceration. The frontal study presents a nodular "intraluminal" type of defect, resembling a polyp, in the distal descending duodenum. This represents nodular invasion by the tumor. Detailed rotation of the patient would have indicated its extraluminal origin (see Fig. 24).

posterior oblique roentgenogram from this point of view.

7. BILIARY TRACT SIGNS

These consist of a large Courvoisier gallbladder and a dilated common duct (Fig. 7 and 22*B*). The latter may produce a double contour on the inner half of the duodenal sweep, especially when the area is compressed. These are signs secondary to a large pancreas in an obstructive location and do not differentiate it from pancreatitis.

A differentiation from carcinoma of the gallbladder depends on the location of the changes. In carcinoma of the gallbladder, the position of the affected duodenum is between the apex of the bulb and the superior flexure, which has a peaked configuration. This segment is elongated, compressed, and infiltrated on its superior and lateral aspect.¹⁴

8. FUNCTIONAL DISTURBANCE

Irregular contractions with marked spasticity and irritability (Fig. 27) associated with periodic retroperistalsis and disordered motor function are prominent. The interval roentgenogram may, on occasion, present a significant gastric or duodenal residue. If such a residue be found without apparent reason, the pancreas should be investigated more thoroughly. A duodenal residue continuing to the 3rd or 4th portion of the duodenum is most significant and indicative of partial obstruction in the vicinity of the angle of Treitz. A malignant

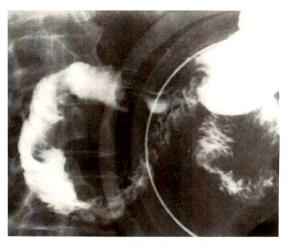


Fig. 24. Carcinoma of the head of the pancreas. Nodular type of intrusion which could simulate an intraluminal polyp if the exposure were made at right angles to this exposure.

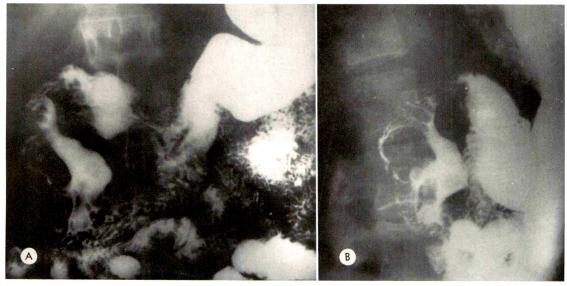


Fig. 25. (A and B) Carcinoma of the head of the pancreas with invasion of the duodenum. There is no enlargement of the retrogastric space. The retroduodenal space is decreased. The wrap-around effect deviates the descending duodenum medially and produces defects in all directions, especially on the medial aspect. The invasive quality of the lesion produces a large nodular defect simulating an intraluminal carcinoma of the duodenum. A polypoid carcinoma of the duodenum does not present any wrap-around effect nor all the other irregularities.

lesion of the pancreas may encircle and invade the lumen at this point (Fig. 29). Functional disturbance alone must never be relied upon for definitive diagnosis. It should act as a stimulus to obtain additional evidence.

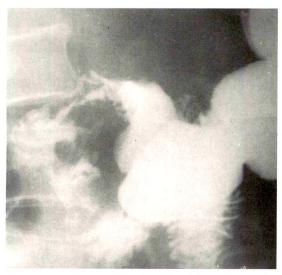


Fig. 26. Carcinoma of the head of the pancreas. The inverted 3 sign is associated with nodular invasion and destruction. Note postbulbar narrowing.

9. THE ROLE OF CINEFLUOROGRAPHY

The prime role of this modality lies in an appreciation of the alterations of the folds

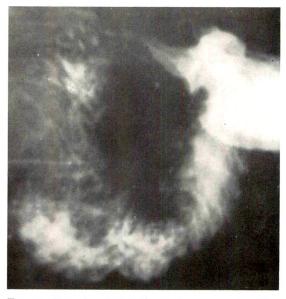


Fig. 27. Functional disturbance is presented with a fleeting appearance of the barium, due to marked irritability and intolerance. Postbulbar narrowing and a small nodular defect at the junction of the second and third portions of the duodenum are noteworthy.

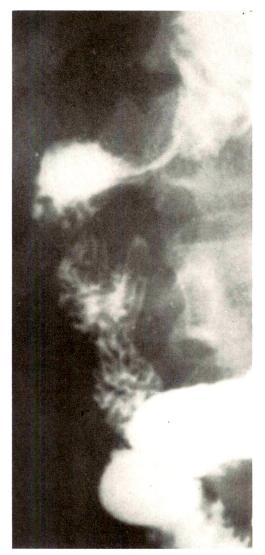


Fig. 28. Carcinoma of the head of the pancreas. The diverticulum is distorted and displaced superiorly.The tumor has extended superior to the antrum, which it indents on the lesser curvature.

of the valvulae conniventes. The marked irritability with skeletonization can be better evaluated. Since these changes consist of fine streaks of barium, high quality cine films are essential. The 70 mm. sequence camera has, therefore, a decided advantage over the 16 mm. or 35 mm. camera.

Cinefluorography is also important in an evaluation of rigidity and fixation of folds. Carcinoma and pancreatitis may simulate each other in this regard. The greater vari-

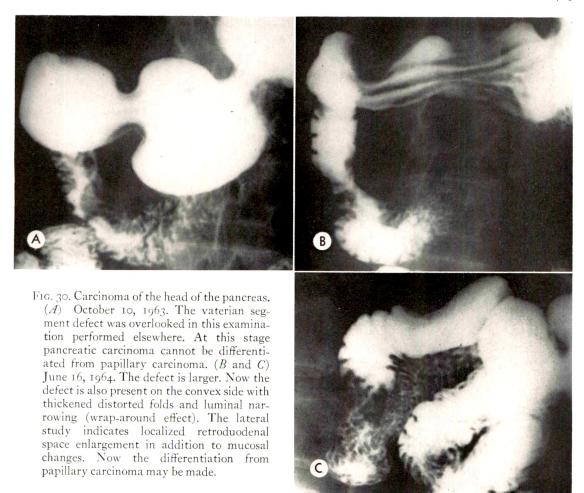
ability, less rigidity and induration, and the absence of fixed corrugations are in favor of pancreatitis. Even in this regard, the 70 mm. sequence camera is preferred, but this may represent an individual bias.

IO. VATERIAN SEGMENT SIGNS

The vaterian segment signs (Fig. 30, A, B and C) have been thoroughly documented by Poppel et al.22 Carcinoma of the papilla or ampulla of Vater may be indistinguishable from carcinoma of the pancreas. Under such circumstances, a diagnosis of a vaterian segment carcinoma is sufficient. A defect in the barium column is present at the papillary site, with the mass being irregular in shape, with considerable effacement, distortion or destruction of the mucosa, and associated with the various other signs presented above. Theoretically, carcinoma of the papilla or ampulla of Vater should produce an intrinsic type of defect in contradistinction



Fig. 29. Carcinoma of body and head of the pancreas. A 2 hour residue study with obstruction at the duodenojejunal junction. The tumor has encircled the bowel, invaded and destroyed the mucosa. The tumor has rotated the stomach along its organic axis so that there is a wide spacing. The angle of Treitz has been uncovered.



to carcinoma of the pancreas. This, however, is not always present, so that additional signs of pancreatic carcinoma are essential for a definitive diagnosis (Fig. 30, A, B and C).

Carcinoma of the duodenum, either with a polypoid defect or a luminal narrowing defect, may usually be readily distinguishable from pancreatic carcinoma in view of the intrinsic intraluminal character of the defect.

The papillary sign of pancreatitis enunciated by Poppel¹⁹ is important in differentiation of carcinoma from pancreatitis.

DISCUSSION

Detailed differential diagnostic evaluation from other disease entities has been amply documented in the literature and

will not be discussed. The purpose of the author has been to present a method of approach to a difficult diagnostic problem in order to improve the accuracy in diagnosis by the general radiologist, who must first suspect the lesion for more detailed study. A constant awareness of the possibility of a relatively silent pancreatic malignancy is essential. To date, the problem of under-reading is more serious than overreading. Once a lesion is suspected, the bidirectional approach will yield a firmer foundation for a roentgen diagnosis. The first question to be answered is, "Does a pancreatic mass exist?" Once this is answered in the affirmative, the more difficult question, "Is the lesion malignant or benign?" must be considered. The geometric approach demonstrates a mass. The

morphologic approach determines its malignant character. Differentiation of carcinoma from pancreatitis may at times be most difficult, if not impossible. The surgeon at the operating table also has his problems in this connection and is not invariably correct.

The role of visceral angiography and its correlation with barium studies will be presented separately.

Percutaneous transhepatic cholangiography, first described by Carter and Saypol³ in 1952, has been revitalized with the advent of television monitoring. This has proved to be a valuable method in the diagnosis of pancreatic disease. Nevertheless, it must be emphasized that barium studies are the first and, therefore, the most important step in the diagnostic armamentarium. Constant awareness of the disease and an appreciation of the bi-directional approach will enable more accurate diagnoses and will indicate the need for more complex procedures when needed.

CONCLUSION

- 1. Although roentgen diagnostic criteria of pancreatic malignancy periodically appear in the literature, a unifying concept of a bi-directional approach has not hitherto been presented.
- 2. The retrogastric and retroduodenal space approach has fallen into disrepute, and a critical re-evaluation has been undertaken in an attempt to re-establish its importance.
- 3. The morphologic criteria have also been divided into subcategories in order to present a cohesive entity.
- 4. Mucosal fold changes have been amplified for recognition of malignant manifestations.
- 5. The wrap around effect is presented, and its significance is emphasized.

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I wish to express my indebtedness to Dr. Maxwell H. Poppel who, throughout the years,

has stimulated my interest in the pancreas, in an appreciation of the subtle manifestations of this enigmatic organ.

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TRANSHEPATIC CHOLANGIOGRAPHY COMBINED WITH SPLENOPORTOGRAPHY IN BILIARY PANCREATIC CARCINOMA*

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PERCUTANEOUS transhepatic cholangiography has been described in numerous recent articles. The diagnostic value of this examination for patients with extraparenchymal obstructive jaundice is well established. However, no reference has been made regarding the combination of this procedure with percutaneous splenoportography in order to more completely delineate the extent of the obstructing process. At the Bronx Municipal Hospital Center, 15 such combined examinations were carried out and they aided in the practical clinical management of these patients.

All of the examinations were elective procedures usually performed just before the exploratory laparotomy for obstructive jaundice. They were done immediately before surgery in order to lessen the danger from bile leakage or hemorrhage. Splenoportography was attempted first and transhepatic cholangiography was undertaken immediately after these serial films had been seen and interpreted. Our technique for performing splenoportography has been previously described.^{3,5} Since there is seldom significant splenomegaly in these patients, autogenous, heat-denatured chromium 51 tagged red blood cells were injected intravenously.7 A scintillation counter was placed in different positions over the left upper quadrant of the abdomen and over the left lower lateral costal margin. Scanning was done and the needle was later directed towards the point of maximum radioactivity.4 When this technique was used, it was always possible to find the splenic pulp with the first puncture. A volume of 40 ml. of 66.8 per cent sodium iothalamate (conray-400) was injected in 10 seconds through an 18 gauge spinal needle. A Stirling, manual, lever operated, pressure injector (Number AD-4740, Charles Thackray, Ltd., Leeds, England) and a 50 ml. plastic syringe (Number 850-S, Becton, Dickinson and Co., Rutherford, N. J.) were used.

During performance of the splenoportography, a radiopaque skin marker was placed over the proposed site of skin puncture for the transhepatic cholangiography. This point was usually 3 cm. below the right costal margin in the mid-clavicular line. When the anteroposterior splenoportograms were examined, the relation of the needle site to the portal vein bifurcation could be seen. This made it possible to direct the 12 cm. 20 gauge spinal needle accurately towards the hilus of the liver where the larger bile ducts are more likely to be found. Following removal of the stylet and attachment of saline filled flexible tubing, the needle was withdrawn from the liver, millimeter by millimeter, until bile was aspirated. As much bile as possible was removed and the biliary tree was filled with 50 per cent diatrizoate sodium solution (hypaque). After sufficient contrast material had been injected during visualization with image intensification, an anteroposterior roentgenogram was taken and the needle was removed. The patient was then maneuvered into various positions to ensure that the ductal system had been completely filled. A roentgenogram is also taken in the

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erect position so that possible filling of the gallbladder takes place.

These two examinations performed together make an accurate anatomic diagnosis possible and also permit an appraisal of the resectability of the lesion. This knowledge, gained prior to exploration, enables the surgeon to plan the approach and the operative procedure in advance. If the splenic or portal veins showed any displacement, deformity or occlusion in the presence of biliary or pancreatic malignancy, the lesion at operation was invariably found to be unresectable for cure.6 The corollary of this may not be true, since many areas of possible metastatic disease, such as the superior mesenteric vein or the inferior vena cava, are not revealed by splenoportography. Hepatic metastases, however, can usually be visualized as filling defects during the venogram phase of splenoportography. In those cases in which biplane splenoportography was performed, the absence of collaterals posterior to the pancreas helped us to assess the nature of the tumor and its extent.5

Our illustrative cases include carcinomas of the hepatic ducts, gallbladder, ampulla of Vater and pancreas. In addition, roent-genograms demonstrating a benign stricture of the ampulla of Vater are presented. The majority of cases were those of carcinoma of the head of the pancreas with complete obstruction of the biliary system.

In our series of patients, the gastrointestinal barium studies made prior to the combined transhepatic cholangiography and splenoportography were not particularly helpful although, in most of the advanced cases of carcinoma of the head of the pancreas, the impression of an extrinsic mass was seen on the loop of the duodenum. Little or no correlation with the upper gastrointestinal series was noted in any of the other lesions mentioned.

ILLUSTRATIVE CASES

CASE I. M.R. (B.M.H.C. 158905), an 88 year old male patient, presented with long-



Fig. 1. Case I. Normal splenoportogram in a patient with carcinoma of the gallbladder. The common hepatic duct was invaded by tumor but the portal vein was not.

standing obstructive jaundice. Splenoportography followed immediately by transhepatic cholangiography was performed before surgical exploration. The splenoportogram (Fig. 1) showed a normal splenic and portal vein but the transhepatic cholangiogram (Fig. 2, A and B) demonstrated a mass invading the common hepatic duct, with evidence of a stone in the distal end of the common bile duct. Dilatation of the ductal system itself was also seen. These studies enabled us to diagnose the correct cause of the obstruction and the presence of the stone. The pancreatic region, we were able to state, was free of pathology. At operation, the patient was found to have a carcinoma of the gallbladder with stones and invasion of the common hepatic duct with obstruction. There was no evidence of extension to the vicinity of the portal or splenic veins.

Case II. C.D. (B.M.H.C. 181658), an elderly woman, also came to the hospital with marked obstructive jaundice. The splenoportogram (Fig. 3, A and B) showed complete obstruction of the splenic vein with collateral veins draining into gastric varices. The transhepatic cholangiogram (Fig. 4, A and B) demonstrated complete obstruction of the common bile duct with dilatation of the ductal system. The characteristic convex contour at the point of obstruction suggested the diagnosis of carcinoma of the head of the pancreas and the splenoportographic findings suggested that the lesion was far advanced and unresectable. At operation, this impression was confirmed.

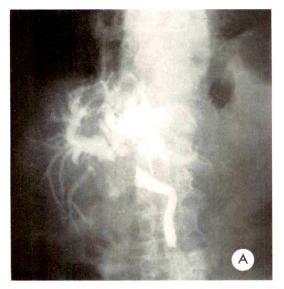




Fig. 2. Case I. (A) Transhepatic cholangiogram and (B) sketch demonstrating carcinoma of the gallbladder with invasion of the common hepatic duct. A stone was found in the ampulla of Vater.

Case III. A.E. (B.M.H.C. 198234), an elderly male underwent combined splenoportography and transhepatic cholangiography for delineation of the cause of severe unremitting jaundice. The splenoportogram (Fig. 5) was entirely negative but the transhepatic cholangiogram (Fig. 6, A and B) showed complete obstruction of the distal common duct. On the basis of these findings we believed that we would find a resectable tumor of the head of the pancreas. At surgery, it was possible to perform a pancreaticoduodenectomy and no evidence of lymph node metastases or tumor extension was found. The operation was quickly performed

because of the advance knowledge of the nature of the lesion and the uninvolved portal venous system.

Case IV. E.W. (B.M.H.C. 263268), a 29 year old Negro woman, was found to have obstruction of the second portion of the duodenum. Jaundice was also present. A splenoportogram (Fig. 7, A and B) demonstrated a hold-up of contrast material at the splenoportal junction. This was interpreted from the anteroposterior and lateral roentgenograms as extrinsic pressure due to pathologic enlargement of the celiac axis lymph nodes. The trans-



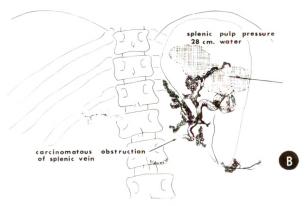
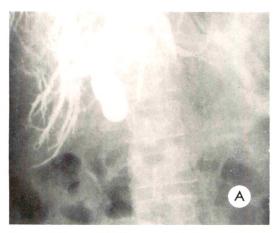


Fig. 3. Case II. (A) Splenoportogram and (B) sketch showing far advanced carcinoma of the head of the pancreas. There is complete obstruction of the splenic vein with gastric varices. Subcapsular extravasation of contrast material is seen in the spleen. Some of the contrast material can be seen to have reached the portal vein.



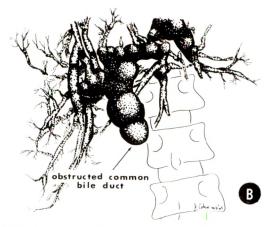


Fig. 4. Case II. (A) Transhepatic cholangingram and (B) sketch showing the complete obstruction of the common bile duct with a characteristic convex contour due to carcinoma of the head of the pancreas.

hepatic cholangiograms (Fig. 8, A, B and C) showed obstruction of the common bile duct with proximal dilatation of the bile ducts and gallbladder. The diagnosis of carcinoma of the ampulla of Vater was confirmed at surgery and although the lesion was technically resectable, the tumor had metastasized to the regional lymph nodes including those surrounding the celiac axis. Several months following the pancreaticoduodenectomy, repeat splenoportography was performed. This showed a recurrence of the obstruction of the splenic vein plus intrahepatic filling defects suggestive of metastatic deposits. This was later confirmed at autopsy.

Case v. R.D. (B.M.H.C. 319910), a 58 year old male had a 2 month history of painless progressive jaundice. The first splenoportography was a technical failure. Transhepatic cholangiography demonstrated distention of the common bile duct with a distal fusiform constriction. There was no evidence of any stones. Because of these findings, we decided to make a second attempt at splenoportography. This proved successful and revealed a normal portal venous system superimposed upon the contrast material remaining in the biliary tree (Fig. 9, A and B). Our diagnosis was that of a carcinoma of the distal common bile duct without metastases or extension. At operation, the sphincter of Oddi was excised locally and no tumor was found. Operative pancreatograms demonstrated that the rest of the pancreatic duct system was normal. The final diagnosis was benign stricture of the ampulla of Vater.

The fusiform rather than blunt convex appearance of the obstructed column of contrast material may have been a clue to the correct diagnosis in this case.

Case VI. A.C. (B.M.H.C. 290787), an elderly male, had combined splenoportography and transhepatic cholangiography prior to surgical exploration for long-standing obstructive jaundice with biliary colic. The splenoportogram (Fig. 10, A and B) was normal except for an obstructed branch of the right portal vein. This was suggestive of an intrahepatic lesion. The transhepatic cholangiogram (Fig. 11, A and B) showed choledocholithiasis and cholecystolithiasis. In addition, irregularities of the gallbladder lumen and partial obstruction of the common hepatic duct were interpreted as indicating malignant disease of the gallbladder.



Fig. 5. Case III. Normal splenoportogram in a patient with resectable carcinoma of the head of the pancreas without evidence of lymph node involvement.

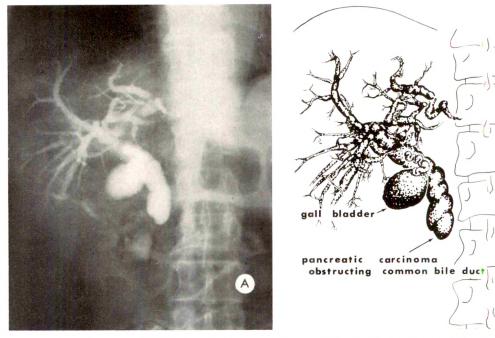


Fig. 6. Case III. (A) Transhepatic cholangiogram and (B) sketch showing typical appearance of the biliary tree in carcinoma of the head of the pancreas.

At surgical exploration, the nature of this lesion and its extension into the liver parenchyma were confirmed.

Case VII. A.W. (B.M.H.C. 297738), an elderly male, had partial obstructive jaundice. The splenoportogram was normal in all respects but the transhepatic cholangiogram (Fig. 12, A and B) showed massive distention of the gallbladder and intrahepatic bile ducts. There was a partial obstruction of the midpor-

tion of the common bile duct and a small amount of contrast material was seen trickling through the area of stenosis into a normal distal duct. At exploration, a carcinoma of the common bile duct was found and it was assessed to be surgically resectable.

DISCUSSION

In all cases in which combined splenoportography and transhepatic cholangiog-

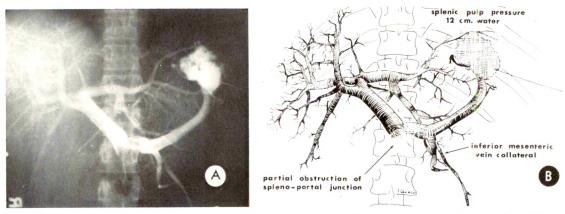
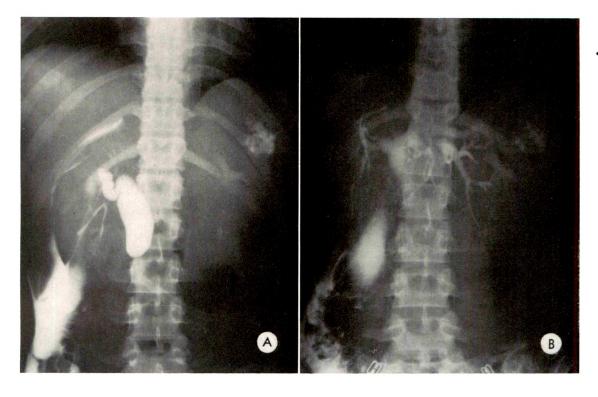


Fig. 7. Case iv. (A) Splenoportogram and (B) sketch demonstrating carcinoma of the ampulla of Vater in a young woman. The lesion was resectable but the metastases to the celiac lymph nodes, shown here as the obstruction at the splenoportal junction, precluded the possibility of a surgical cure.



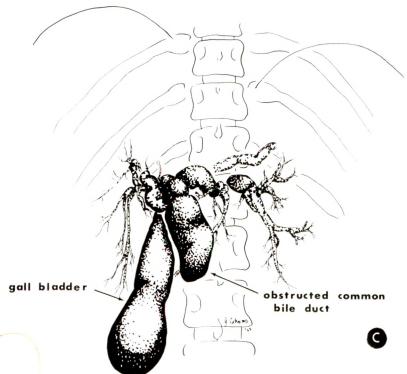


Fig. 8. Case IV. (A and B) Different views and (C) composite sketch of the transhepatic cholangingram showing the dilated gallbladder and total obstruction of the common bile duct secondary to carcinoma of the head of the pancreas.

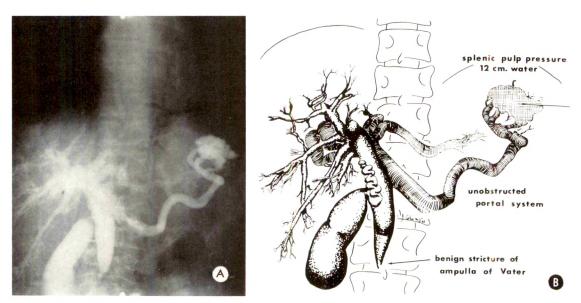


Fig. 9. Case v. (A) Splenoportogram superimposed on the transhepatic cholangiogram and (B) sketch demonstrating what later has proven to be a benign stricture of the ampulla of Vater. The splenoportogram was normal in all respects.

raphy was used, an accurate diagnosis and assessment of the extent of the lesion were provided by this approach. Most of these patients are elderly and, in general, poor operative risks. Therefore, a roentgenologic technique which can help the surgeon avoid a time consuming but futile mobilization of the head of the pancreas is worth pursuing. Splenoportography is a particularly sensitive procedure for detecting the growth and spread of tumors of the pancreas and biliary tree. By itself, however, a splenoportogram can not delineate the site of the primary

tumor causing the biliary obstruction nor can it distinguish malignant from inflammatory displacement or obstruction of the portal venous pathways. Neither can transhepatic cholangiography alone reveal intrahepatic, periportal or celiac axis metastases.² In combination, however, these two examinations complement each other and are synergistic in the sense that more information can be gained from their combined use than the simple sum of the data obtained from each when used separately. In our series of cases, all degrees of involve-

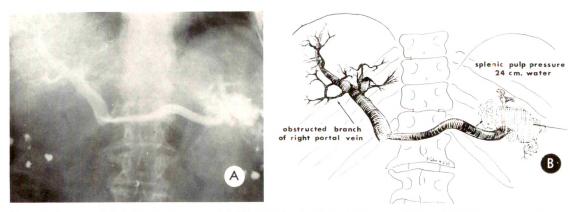


Fig. 10. Case vi. (A) Splenoportogram and (B) sketch, showing carcinoma of the gallbladder extending into the liver and obstructing a branch of the intrahepatic portal vein.

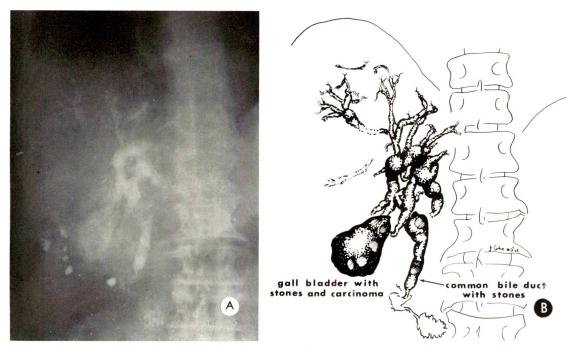


Fig. 11. Case vi. (A) Transhepatic cholangiogram and (B) sketch demonstrating that, in addition to the cholelithiasis and choledocholithiasis, there are irregularities of the gallbladder contour suggestive of neoplasm.

ment of the portal system associated with pancreaticobiliary carcinomas were noted. In all of the cases where any abnormality of the portal system was seen, from slight external compression (Fig. 7A) to complete obstruction (Fig. 3A), the tumor was found

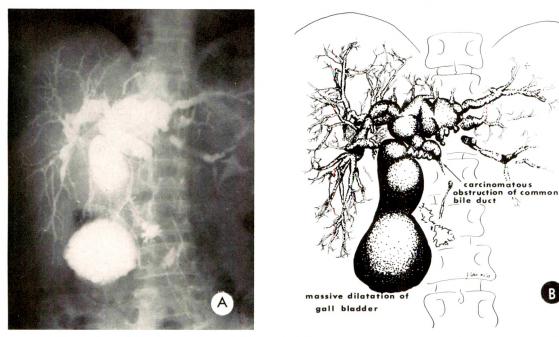


Fig. 12. Case VII. (A) Transhepatic cholangiogram and (B) sketch showing a resectable carcinoma of the common bile duct causing a partial obstruction.

to be too far advanced for curative resec-

CONCLUSIONS

Splenoportography combined with transhepatic cholangiography has been found to be of definite clinical value in determining the cause of obstructive jaundice and in estimating the resectability of biliary pancreatic carcinomas.

A series of 7 cases illustrating the value of the combined studies is presented.

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ATTEMPTS TO IMPROVE IODIPAMIDE INTRAVENOUS CHOLANGIOGRAPHY*

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IMPROVEMENT of intravenous cho-langiography could be sought in a number of ways. Since biliary duct visualization depends upon the concentration and amount of the iodine containing cholangiographic agent in the bile, better duct visualization might be attained by stimulation of the liver to excrete the agent in higher concentration, or by increasing the amount of agent presented to the liver. The first possibility was investigated using sodium dehydrocholate, cortisol, and triiodothyronine, each of which had been suggested to be of value in increasing the liver's excretory capacity. The second possibility was studied by increasing the size of the injected dose and by attempting to decrease the loss of the cholangiographic agent in the urine by administering renal tubular blocking agents.

A third possibility for obtaining better radiopacification of the bile ducts which was investigated was the simultaneous excretion of two different contrast agents. Also thought worthy of study was the excretion of the cholangiographic agent during different states of body hydration.

EXPERIMENTAL DESIGN

Mongrel dogs, weighing 10.8 to 20.4 kg., previously cholecystectomized and having had a T-tube placed in the common bile duct, were fasted over night but allowed water. The dogs were in good health and had normal liver and biliary tract function on the basis of histologic, biochemical and roentgenologic evidence. Other details of the experimental technique are described in a previous paper.

Experiments were performed at two dose levels of iodipamide methylglucamine 52 per cent (cholografin methylglucamine),

o.3 and c.6 ml./kg. of body weight given as a single rapid dose intravenously. Each milliliter contains 520 mg. of iodipamide compound, with iodine content per ml. of 260 mg. The dose of 20 ml. for clinical use is .29 ml./kg. body weight for a 70 kg. man. In each experiment the injection of iodipamide and the collection of bile were exactly the same, the addition of the test drug or the modifying of the state of hydration being the only known change of the procedure.

Twenty to 50 μ c of radioactive iodipamide methylglucamine was injected with the standard iodipamide. The percentage of iodine in the bile was determined from the relation of radioactivity in the bile to the radioactivity and the known iodine content of the original injected solution. The iodine per cent gives a direct measure of the radiopacity. Comparisons of the tested substances and the controls were charted on graph paper.

The groups of experiments were performed as follows:

- I. To stimulate the liver to increase the concentration of cholangiographic agent in the bile.
- a. Cortisol: Three dogs receiving cortisol were tested at 0.3 ml. and 3 at 0.6 ml./kg. body weight of iodipamide. Each dog received at least two intravenous injections of 25 mg. of sodium succinate ester of hydrocortisone (Solu Cortef) and 3 dogs received 3 injections each, the injections being timed 30 minutes before, at the same time, or 30 minutes after the cholangiographic agent. Each injection was 1.3 to 1.8 mg. per kg. body weight of cortisol preparation.

b. Sodium dehydrocholate: Three dogs were tested at the 0.3 ml./kg. level of iodi-

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pamide, and 4 tests were performed in 3 dogs at the 0.6 ml. level. Sodium dehydrocholate (decholin) as a 20 per cent aqueous solution was given intravenously a few seconds preceding iodipamide, the dose being 25 to 30 mg./kg. of body weight.

c. Tri-iodothyronine: Two dogs were given 18 µg. of tri-iodothyronine per kg. of body weight daily by mouth for 11 to 15 days and then tested with 0.3 and 0.6 ml./kg. doses of iodipamide.

II. To increase the amount of agent presented to the liver.

a. *Probenecid:* A 10 per cent solution of p-di-n-propylsulfamylbenzoic acid (benemid) was given to 2 dogs receiving 0.3 ml. and 2 receiving 0.6 ml. iodipamide per kg. of body weight. The probenecid dosage amounted to 55–65 mg./kg. body weight and was given a few seconds preceding the cholangiographic agent.

b. Methylglucamine diatrizoate: The doses of iodipamide and methylglucamine diatrizoate were given together as prepared solution (duografin) to 6 dogs. Three dogs received 0.8 ml. and 3 received 1.6 ml./kg. of body weight of the mixture, the lower dose being equivalent to 0.3 ml./kg. iodipamide and 320 mg./kg. diatrizoic acid, the higher dose being equivalent to 0.6 ml./iodipamide and 640 mg./kg. diatrizoic acid.

III. To test simultaneous biliary excretion of 2 contrast agents: A rapidly absorbed oral cholangiographic agent was administered by stomach tube with 200 ml. water. At the 0.3 ml./kg. dose of iodipamide, 13 studies were performed, 2 by giving the oral agent 40 minutes after, and 11 by giving the oral agent approximately 2 hours before the intravenous cholangiographic agent. At the higher iodipamide dose level, 12 studies were made with the oral agent being administered 2 hours before the intravenous agent. In 3 of the trials, bunamiodyl was the oral agent. Calcium ipodate 3 gm. was used in the remainder, the oral dose being 162 to 213 mg./kg.

IV. To investigate the relation of body hydration to excretion of the cholangiographic agent: Two dogs were kept without food or water for 48 hours preceding an iodipamide injection of 0.3 ml./kg., and 3 dogs were similarly treated preceding an injection of 0.6 ml./kg.

The same dogs were tested for comparison under two other regimens: (1) in which water was allowed *ad libitum* but food was withheld for 12 hours, and (2) in which food was withheld for 12 hours, while water was allowed *ad libitum* and then 200 ml. of water was given by stomach tube I hour prior to iodipamide.

RESULTS

The results in the groups of experiments were as follows:

- I. To stimulate the liver to increase the concentration of cholangiographic agent in the bile:
- a. *Cortisol:* With the timing and the amounts injected, cortisol had no effect on the bile iodine values at the 0.3 ml./kg. and 0.6 ml./kg. dose level of iodipamide.
- b. Sodium dehydrocholate: At the 0.3 ml./kg. level of iodipamide, injection of sodium dehydrocholate depressed the bile iodine values during the first 30 to 45 minutes after simultaneous injection (Fig. 1). At 1 hour the iodine in the bile was the same. At 1½ to 3 hours, the bile iodine in the decholin treated animals was slightly higher than in the controls. Bile iodine values for the 0.6 ml./kg. doses were not obtained, but the similarity of bile-blood ratios at 0.3 and 0.6 ml./kg. doses suggests that the same relationships would hold true at the larger doses.
- c. Tri-iodothyronine: Bile iodine concentrations in dogs receiving tri-iodothyronine were not significantly different from control values. Although at the 0.3 ml./kg. dose level of iodipamide, the curves suggested an augmented excretion of iodine into the bile, the opposite was true at the 0.6 ml./kg. level.
- II. To increase the amount of cholangiographic agent presented to the liver.
- a. *Probenecid*: Bile iodine concentrations in the dogs receiving probenecid were

depressed at all times as compared to controls at both the 0.3 and 0.6 ml./kg. doses of iodipamide (Fig. 2, A and B).

b. Methylglucamine diatrizoate: At the 0.3 ml./kg. dose of iodipamide, there was probably no valid difference between the bile iodine values of the animals receiving diatrizoate and those of the controls. At the 0.6 ml./kg. level, the bile iodine studies were not obtained but the bile-blood ratios indicated that the results would not have differed significantly from the curves at the lower doses. Certainly, no higher iodine concentrations were obtained in the bile and actually they might have been depressed in the early time period.

III. To test simultaneous biliary excretion of 2 contrast agents: Administration of an oral cholangiocholecystographic agent (ipodate or bunamiodyl) 40 minutes after the intravenous iodipamide resulted in decisively lowered bile iodine values at $1\frac{1}{2}$ to $3\frac{1}{2}$ hours, but essentially the same bile iodine values were noted during the first hour (Fig. 3). When the cholegraphic agent was administered to the dog 2 hours before

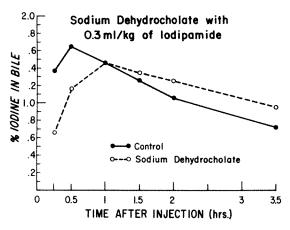


Fig. 1. The administration of sodium dehydrocholate with iodipamide depressed the biliary excretion of iodipamide at one-quarter to one-half hour after simultaneous injection of the two compounds. The late increased excretion of iodipamide in the dehydrocholate tests may have been due to higher blood levels of contrast medium persisting longer because of earlier lessened excretion. The depression of iodipamide is thought to be due to competition between dehydrocholate and iodipamide for the same liver excretory mechanism.

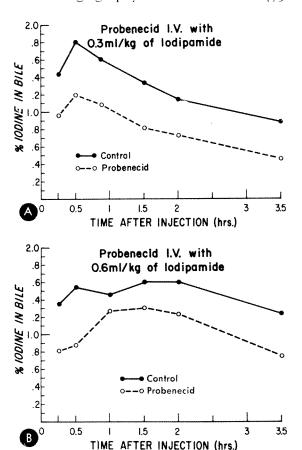


Fig. 2. (A and B) The administration of probenecid with iodipamide depressed biliary excretion of iodipamide at all times during the 3½ hour test period, both at (A) 0.3 ml./kg. dosage and (B) 0.6 ml./kg. dosage. Probenecid is thought to compete with iodipamide for excretion by the liver. Probenecid appears to be incapable of blocking the renal excretion of iodipamide.

the intravenous iodipamide, bile iodine concentrations were depressed during the entire observation period at the 0.6 ml./kg. dose level. With the 0.3 ml./kg. dose, the depression was less striking but still significant until the $3\frac{1}{2}$ hour time, when values were the same as those in the controls (Fig. 4, A and B).

IV. To test the relation of body hydration to biliary excretion of the cholangiographic agent: Subjecting dogs to rigorous dehydration (48 hours) resulted in no clear-cut differences in the bile iodine values following iodipamide injection compared to (a) dogs allowed water *ad libitum* or (b)

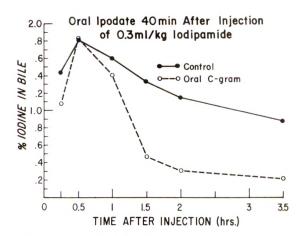


Fig. 3. The administration of an oral cholangio-cholecystographic agent 40 minutes after the intravenous injection of iodipamide resulted in decisively depressed biliary iodipamide at the 1½ to 3½ hour test times. The time of biliary iodipamide depression correlates with the time when the oral cholegraphic agent was probably being maximally excreted, and, therefore, the time when the two contrast agents were competing for liver excretion.

dogs allowed water ad libitum and then given additional water by stomach tube immediately before injection. At the 0.3 ml./kg. dose level of iodipamide, the dehydrated dogs had essentially the same bile iodine values as the dogs allowed water ad libitum, and giving the dogs extra water seemed to give lower bile iodine values. At 0.6 ml./kg. dose of iodipamide, the bile iodine values in the dehydrated dogs and in the dogs given extra water were almost identical, while the control dogs had lower iodine values.

DISCUSSION

Cortisol failed to influence favorably the excretion of iodipamide. The trial of cortisone on iodipamide excretion was suggested by the report that cortisone possessed choloretic and hydrocholoretic properties when utilized in patients with jaundice due to hepatitis. Other work has failed to show any value of cortisol in acceleration of the plasma clearance of bromosulfophthalein or the percentage disappearance rate of I¹³¹ labelled rose bengal from the plasma,

nor did hydrocortisone alter the volume, bilirubin concentration, or total bilirubin output.² The present study is consistent with these latter data.

The failure of sodium dehydrocholate to enhance the hepatic excretion of iodipamide and, in fact, to depress the excretion is no surprise if the behavior of sodium dehydrocholate in relation to other compounds excreted by the liver is studied. It is probable that there is competition between the iodipamide and sodium dehydrocholate just as there has been demonstrated to be

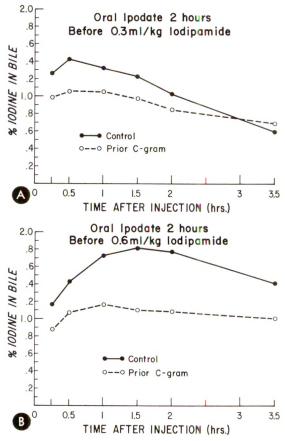


Fig. 4. (A and B) The administration of an oral cholangiographic agent 2 hours before the intravenous injection of iodipamide resulted in depression of biliary iodipamide excretion at dose levels of (A) 0.3 ml./kg. and (B) 0.6 ml./kg. of iodipamide. The absorbed oral agent was thought to be in competition with the iodipamide throughout the entire test period, since the oral agent (ipodate) was probably being excreted into the bile during this time by reason of its prior administration.

competition between dehydrocholic acid and bromosulfophthalein, and rose bengal dye^{3,11} and bromosulfophthalein and probenecid. The interference phenomenon between an oral cholecystographic agent and bromosulfophthalein has been observed, to another the blood bilirubin level has been noted to be elevated following the ingestion of a cholecystographic agent. The competition between two or more compounds for excretion into the bile may occur in their uptake from the plasma by the liver or in the conjugation step within the liver of the compounds with glucuronide or with cystein. 9

The trial of tri-iodothyronine was prompted by the report of increased hepatobiliary clearance of bromosulfophthalein by improved removal efficiency in hyperthyroidism. The tri-iodothyronine medicated dogs' inability to excrete additional iodipamide into the bile might have been due to the dogs not having reached a suitably high state of hypermetabolism, or the inability of tri-iodothyronine to reproduce all the characteristics of the naturally occurring hyperthyroid state, or due to different handling of iodipamide and bromosulfophthalein.

The idea of improving opacity of the bile ducts in cholegraphy by reducing the renal excretion of iodipamide and, therefore, offering more contrast medium to the liver is based on the work of Edling and Helander.5 They reported a higher density of contrast medium in the bile ducts when paraminohippuric acid or a combination of penicillin and N,N'-dibenzylaethylendiamine, compounds known to depress the tubular excretion of contrast medium, were injected with iodipamide than in patients injected with iodipamide alone. In rabbits, however, under laboratory controlled conditions a similar dose of paraminohippuric acid (0.024 to 0.034 gm./kg. body weight) did not raise the iodine concentration of common duct bile, or decrease the renal excretion of the contrast medium.12 A deeper look into the problem gives information which explains the inability of sub-

stances which depress tubular excretion to increase the level of iodipamide in the bile. The depression of tubular excretion of a contrast medium by probenecid may occur, but this should be of little importance since, at the plasma levels of contrast media encountered in clinical excretory urography and cholangiography, a very high percentage of the contrast medium is excreted by glomerular filtration and very little by tubular activity.¹⁴ Also, probenecid inhibits the excretion of bromosulfophthalein and bile pigments by the liver, 16 evidently because of a competitive inhibition mechanism. With both, diatrizoates and iodipamides, renal excretion is predominantly by glomerular filtration, and the renal excretion of one evidently has no influence on the other. A further fallacy in attempting to improve cholangiography by blocking renal excretion was revealed by a study of the relation of dose to excretion of iodipamide in which it was found that bile-blood ratios of iodipamide and the biliary iodine concentrations did not reach a higher peak following increase of the iodipamide dose above 0.3 ml./kg. body weight, although these higher levels were somewhat more prolonged by the larger doses.7 The advantage to be gained by offering increasing amounts of cholangiographic agent to the liver then is relatively little.

The diminished excretion of iodipamide when an oral cholecystographic agent, either bunamiodyl or ipodate, is given is another example of competition of two compounds for the hepatic excretion mechanism. The present study offers data on the bile levels of iodipamide, but not on the output of the oral cholangiographic agent so that it is not known whether the biliary output of ipodate or bunamiodyl was reciprocally depressed by the iodipamide. A recent clinical study in which iodipamide was injected following the ingestion of ipodate resulted in a failure of the intravenous cholangiographic agent in a large number of patients, instead of affording cumulative opacity and better visualization as was hoped for.8

It had been suggested that dehydration would favor the obtaining of better intravenous cholangiograms, similar to the traditional policy in which patients undergoing excretory urography are subjected to dehydration with the expectation that the contrast material in the urine will be more concentrated and result in better demonstration of renal structures. Compared to the kidney, the liver plays an insignificant part in excretion of water and in regulation of fluid and electrolyte balance. Water is considered to be filtered through the hepatic laminae, and not actively secreted by hepatic cells.4 The failure to improve the excretion of iodipamide in the bile during a long period of dehydration, such as could be imposed on the experimental animal, indicates that there is no need to withhold fluids from the patient about to undergo intravenous cholangiography. Likewise, no advantage of giving additional fluid at the time of cholangiography could be deducted from the present study.

If intravenous cholangiography is to be improved, we must look elsewhere than to the attempts described, all of which have been unsuccessful. It is unlikely that liver excretion can be enhanced by other drugs. Possibly another cholangiographic agent could be found which could be used in conjunction with iodipamide while not offering competition to it, but this too is unlikely. The most logical approach would be to find a compound which would be excreted into the bile by ordinary hepatic mechanisms, a compound which would be excreted with the same efficiency as iodipamide but having a higher iodine content, or a compound of essentially the same iodine content as iodipamide which would be excreted in higher concentration into the bile.

SUMMARY

To improve intravenous cholangiography, efforts were made (a) to stimulate the liver pharmacologically in order to excrete more of the contrast medium, iodipamide, (b) to offer to the liver more iodipamide by attempting to block its renal excretion, (c)

to cause the liver to excrete two cholangiographic agents, one oral and one intravenous, simultaneously, and (d) to determine if the state of body hydration can influence biliary excretion of iodipamide. None of these measures resulted in greater excretion of the contrast medium into the bile. With the administration of probenecid, dehydrocholic acid, and an oral cholangiographic agent, the biliary levels of iodipamide were actually depressed, probably because the two substances being handled simultaneously competed for a liver excretory mechanism

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FLAVORING BARIUM SULFATE*

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MOST patients no longer expect barium sulfate suspensions to taste chalky or unpleasant. Many radiologists and hospital pharamacists can easily improve this aspect of gastrointestinal examinations.

Oral suspensions should be sufficiently palatable so that they will be taken readily by the patient. Disagreeable suspensions often tempt the patient to hesitate and not take the suspension as requested. This prolongs the examination and increases the radiation exposure to both doctor and patient. If the suspension is too obnoxious it may cause nausea, retching, or vomiting and complete refusal by the patient. Spoiled suspensions are particularly prone to do this. Often children cannot be induced to take a second swallow of a repulsive suspension and it is not quite reasonable to insult sick children's taste buds.

The first and most important principle is to eliminate the chalk or mud-like texture that makes the suspension unpalatable. This is easily accomplished by the addition of a good suspending agent such as sodium carboxymethylcellulose or some of the many vegetable "gums" such as pectin, acacia and tragacanth. Because of the great variety and types of these agents available. almost any viscosity level can be obtained; but too thick or excessively paste-like textures, similar to thick cream or butter, will severely limit the amount of suspension that the patient will willingly swallow. Almost all of the present day barium contrast products have such suspending aids already in them whether listed on the container labels or not. Therefore, one must be extremely cautious in adding another suspending aid to these preparations since their viscosity can increase quite rapidly with extremely small additions.

The second principle to follow is to tailor the suspension flavor for the in-

tended consumer. Is it to be taken by adults, children or both? Children usually like a decidedly sweet flavor, but the average adult does not. One of the most popular flavors for children is sweet cherry. Raspberry and sweet orange are also well liked. Wright²¹ flavor tested over 600 adults. Their choices, purely for taste alone in descending order, were the syrups of cocoa, raspberry, orange, cherry, sasparilla, citric acid and aromatic syrup of eriodictyon.

The all-around efficient flavoring agents for disguising bitter, salty and other unpleasant tastes, such as occurs with some preservative agents, were the syrups of cocoa, raspberry and aromatic syrup of eriodictyon.

A basic barium suspension with a mild sweet cherry or raspberry flavor can be made for general use and other flavors added as they are chosen by the child or adult patient. A 10 to 1 or higher mixture of cherry with wild cherry is usually better liked than either alone. Some "Kool-aid" or other instant drink flavor can then be added just before the patient drinks the suspension. The radiologist or his pharmacist must decide what brand and type flavors he wants to use and then make some experiments to see if they are compatible with the other substances or additives present and to determine the quantity of sweetening agents that must be added to the basic suspension. A noncaloric type is best and a I to 10 mixture of saccharin and sodium cyclamate has proved satisfactory. Sugar and true syrups are generally to be avoided, because barium suspensions are often given to diabetic patients. Chocolate or cocoa should usually be avoided also because some people do not like it, some are allergic to it, and it can always be added at the last moment if desired.

The third principle often followed by

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flavor experts is to use mixtures. Experience has shown the author that a mild mixture of flavors is best if the radiologist wants to avoid the trouble of regularly adding another flavor at the time of the examination. A mild mixture of three or four flavors such as sweet cherry, wild cherry, raspberry and orange with some vanilla and then a little of a more sharp flavor such as peppermint, lime, apricot, or citric acid has been quite satisfactory. A moderate mixture of various flavors allows the person swallowing the barium suspension to "selectively taste" and pick out the flavor he likes best—if no one flavor, sweetness or texture is predominant. Aromatic powder N.F. containing cinnamon, ginger, cardamon seed and nutmeg is a pleasant flavoring powder with the mixture principle that also can be used by adding 3 gm. of the finely powdered mixture to each kilogram of barium sulfate and mixing thoroughly.

The flavors chosen for a suspension must also disguise the other ingredients of the suspension such as preservative and suspending agents. Masking these additives may even determine some of the flavors.

The location of the radiological laboratory where the suspension is to be used may also influence the choice of flavors since local tastes and customs vary. A strong anise or licorice flavor may be fine in Ankara, Turkey, but not so well received in Kokomo, Indiana. From personal experience, the author can testify that an otherwise fine flavor is not well tolerated if the patients associate its accompanying aroma with a similar one found in the local popular toilet bowl cleanser. A mild but agreeable aroma is pleasant and quite often is a by-product of the flavoring agents. A pleasant odor is particularly desirable in suspensions that are used for barium enemas.

The radiologist, his pharmacist, or the manufacturer must decide whether to use liquid or powdered flavors. This choice is usually made to conform to local mixing or other processing equipment, convenience and cost. Either type flavor can be satisfactory, but a word of caution is necessary.

Fine powders adhere to coarser particles when they are mixed together. This can have an effect on taste because the finer material adsorbed on the coarser may cause a change in flavor. For example, when paprika and sugar are mixed, if the sugar is extra fine and the paprika relatively coarse, the first taste of this mixture will be sweet. When the sugar is coarse and the paprika extra fine, the mixture will not have the sweet taste. The finer powder in each case has coated the coarser and determined the taste.

Relative small amounts of liquid flavors can be sprayed into the powdered barium and then mixed well to form a "dry" product. This is sometimes desired for prolonged storage, convenient packaging or shipment.

Some pharmaceutical manufacturers have "taste panels" of several people to taste test their products. These people are carefully recruited from employees and their children. In most commercial concerns, the flavoring of their product is a "top trade secret"known only to a few individuals and jealously guarded. "Coca-Cola" is an example and, of course, is a mixture. If the radiologist will try some mixtures and test only two or three at a time, he should soon be quite successful. He can recruit or draft a taste panel from x-ray technicians, students, or employees and develop a highly acceptable taste for his locality. The taste panel, however, should not be a haphazard selection, but should follow rational rules such as those given by Moir.19

The radiologist should realize that the popularity of flavors changes from time to time, and that there are many reasons for a variance in an individual's taste ability and choice of flavors. For example, some people are "nontasters" and some tastes are different partly because of different solubilities in different salivas. Taste thresholds also vary. They have been correlated by Griffin and Fischer^{8,12} with salivary oxidation rates and inversely correlated with salivary catalase activity.

Kaplan and his co-workers15 tested 121

subjects with duodenal and stomach ulcers and found that taste differed and was more sensitive in those patients who had the duodenal ulcers than in those with the stomach ulcers.

Henkin and Powell¹⁴ found that patients with cystic fibrosis were much more sensitive to taste. They could detect all substances at concentrations 40 to 13,000 times more dilute than the concentrations at which the same substances could be detected by normal volunteers. On the other hand, there is a significantly higher percentage of nontasters among persons with nodular goiter than normal controls.¹³ Fallis *et al.*⁷ reported decreased acuity for sodium chloride in hypertensive patients.

There is also a relationship between non-tasters and parents of Mongols, and between taste thresholds and the amount of cigarettes smoked.⁸

There is also a variation in tastes and a relationship between nontasters and race. Among Brazilian Indians, only 1.2 per cent, and among Navahoes, Cree and Beaver Indians only 2.0 per cent are nontasters; but Bombay Indians reach a high of 42.5 per cent. The rate of nontasters is less than 2 per cent for some American Negroes, 7 per cent among Japanese, 17 per cent for Welsh and 30 per cent for Western Europeans and Caucasians in general.^{2,17} Taste sensitivity also varies with age and sex for different sweet, sour, salty and bitter substances.11 Females are more sensitive tasters in all ages. Taste sensitivity in both sexes gradually rises from infancy to a peak at the ages of 16 to 20 years and thereafter declines. The decline is much more rapid for males. Cooper, Bilash and Zubek⁶ have shown that apparently some individuals have a delayed peak for sour, sweet and bitter substances. These sensitivities declined only after reaching peaks in the 30 to 34 year age groups. Sensitivity for all modalities declined after 50 years in both male and females. Sensitivity to common table salt, however, was found to decline consistently with increasing age.

Taste may also vary because of a difference in anatomy. The taste receptors for

bitter occur on the upper surface at the back of the tongue, and those for sour occur primarily at the sides. Anatomic investigations have shown that the gustatory papillae reach full development at puberty, and several studies have demonstrated that in adult life the number of taste buds tend to decrease with age. Children have taste buds studding the hard palate, walls of the throat, and the central upper surface of the tongue. By maturity, however, most of the taste buds are lost from these areas. During normal aging, many of the remaining taste buds disappear.

Many of these taste differences can be explained on the basis of heredity. Blakeslee⁵ and Fox¹⁰ demonstrated that the ability of persons to taste phenylthiocarbamide and other substances is heritable as a mendelian recessive. Even those who get any taste at all from the phenylthiocarbamide describe it variously as bitter, sweet, salty or sour.

Fallis, Lasagna and Tétreault⁷ taste tested thresholds in 20 subjects for sodium chloride dissolved in distilled water and found some subjects identifying the solutions as "quinine water," "Epsom salts" and other substances. Moir¹⁹ tested 60 persons as to their ability to recognize by taste 4 simple flavors—orange, lemon, lime and vanilla. Only 1 person had a perfect score. Five had records of over 75 per cent, but 48 failed to reach 50 per cent. Vanilla was variously identified as black currant, lime, apricot, greengage, damson, lemon, pineapple, orange, tangerine, almond, red currant and strawberry.

It is not only taste ability and sensitivity that influence food and flavor likes and aversions, but these are further influenced by cultural, social and idiosyncratic variables. Smith, Powell and Ross²⁰ found that there are more food dislikes among neurotic and anxious individuals than among more normal people. Those individuals with siblings, especially older siblings, have more food dislikes as well as those who do not attend church regularly. Also females have more food dislikes than males.

Some of the idiosyncratic variations that

occur in taste thresholds are due to hormone therapy, the ingestion of aspirin, the first 3 days of menstruation, stressful situations and pregnancy.^{9,16}

SUMMARY

Because of many variations in different people, flavor likes and dislikes are apt to differ. It is quite evident, then, that the radiologist will never find a flavor or combination that will please everyone. Nevertheless, he should not be discouraged from flavoring his barium suspensions and trying to find better flavor combinations. By doing this, through some of the methods suggested here, the radiologist can succeed in making gastrointestinal examinations much more pleasant for the great majority of his patients.

The main principles to follow in flavoring barium sulfate suspensions are:

- 1. Eliminate the chalk-like texture by the addition of a good suspending or dispersing agent.
- 2. Do not make the suspension too vis-
- 3. Use a mixture of flavors so that no one flavor, sweetness or texture predominates.
- 4. Test a few different mixtures on several carefully selected sensitive tasters chosen from the local laboratory.

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TOXICITY STUDIES ON TANNIC ACID ADMINISTERED BY ENEMA*

I. EFFECTS OF ENEMA-ADMINISTERED TANNIC ACID ON THE COLON AND LIVER OF RATS

By OSCAR N. RAMBO, M.D., F. FRANK ZBORALSKE, M.D., PHILLIP A. HARRIS, PHARM.D., SIDNEY RIEGELMAN, Ph.D., and ALEXANDER R. MARGULIS, M.D. SAN FRANCISCO, CALIFORNIA

ANNIC acid possesses physicochem-TANNIC acid possesses relical properties that are generally considered to make it a valuable adjuvant to the barium sulfate examination for roentgen diagnosis of disease of the colon. Whether introduced before or with the contrast medium, tannic acid alone or in proprietary solutions stimulates peristaltic emptying of the colon, precipitates mucin, and probably suppresses mucus secretion. A preparatory enema containing tannic acid and a peristaltic stimulant is said to aid in clearing the colon of fecal matter and mucus deposits, leaving a clean mucosal surface. The subsequent barium sulfate contrast study discloses fine mucosal detail and makes possible detection of extremely small polypoid lesions and ulcers.

Thomas, in 1963, estimated that tannic acid was used as an adjuvant for more than 25 per cent of the barium enemas administered in this country. The recommended concentrations of tannic acid range from 0.25 to 3.0 per cent.8 Recently, McAlister, Anderson, Bloomberg, and Margulis⁷ and Lucke, Hodge, and Patt⁶ have reported the deaths of 8 patients following multiple tannic acid enemas. The patients died 2 to 7 days after barium tannic acid enemas and their livers showed evidence of centrolobular hepatic necrosis similar to that described more than 2 decades ago by Wells, Humphrey, and Coll¹⁰ in patients dying $3\frac{1}{2}$ to 5 days after tannic acid treatment for extensive burns. To supplement their clinical observations, Wells's group gave subcutaneous injections of tannic acid to rats. In these, the degree of central zone hepatic necrosis varied with the total dose of tannic acid. In 1943, Barnes and Rossiter³ demonstrated that in animals tannic acid produced liver damage when given intravenously or applied to artificial burns.

The use of tannic acid as an adjuvant to the diagnostic barium enema has been predicated on the belief that the solutions are so dilute and so rapidly expelled that they are harmless. No studies on animals, however, have been specifically directed toward establishing whether hepatotoxic levels can be achieved by rectal administration of tannic acid. This investigation was undertaken to define the parameters within which tannic acid can produce hepatotoxicity by this route of administration. This study undertook:

- I. To develop a technique of enema administration that most closely simulates the degree of colonic distention and mucosal exposure to liquid medium encountered in cleansing and diagnostic enemas of humans.
- 2. To determine the concentration of tannic acid necessary to produce hepatic damage under certain standard conditions and to attempt to specify the relationship between the degree of damage, the tannic acid concentration used, and the time of contact.
- 3. To determine the effect of tannic acid on colonic mucosa and to attempt to relate any such changes to the occurrence of liver damage.

Supported in part by a grant in aid from Barnes-Hind Pharmaceuticals, Inc.

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- 4. To investigate the effect of repeated enemas.
- 5. To determine if clysodrast* or tannic acid differ significantly in their effects on colon and liver.

MATERIALS

Female rats (Long-Evans strain), between 40 and 70 days old, ranging in weight from 100 to 170 gm. were given food and fluid *ad lib*. Tannic acid (Mallinckrodt) and clysodrast were studied and the various concentrations were obtained by dissolving measured amounts in water.

METHOD

Each rat was placed in a plexiglass tube which was closed at one end by a perforated plate (Fig. 1). Since the animals always attempted to go through the transparent barrier, no limb restraints were needed. A No. 8 Foley catheter (Bardex) was inflated in the rectum to prevent evacuation of the enema. The volume of the enema administered was invariably 3.6 ml. Fluoroscopy and roentgen studies after barium sulfate enemas to rats of this size demonstrated that this volume only slightly distended and completely filled the colon, including the cecum, without reflux into the ileum. The enema was injected through the catheter by syringe. Controlled minimum retention times were I minute or I hour. Serial roentgen studies utilizing tannic acid containing tracer amounts of barium sulfate in 10 rats indicated that most animals retained variable amounts of the enema for 10 to 30 minutes after this forced retention period (Fig. 2, A–D).

Animals serving as controls received saline or water enemas under the same experimental conditions. Additional controls were untreated and in some only the Foley balloon was introduced and inflated. The concentrations of tannic acid and tannic acid in clysodrast ranged from 0.1 per cent to 16 per cent.

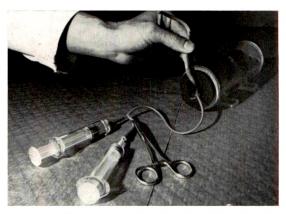


Fig. 1. Method of restraining rat in plexiglass tube while administering enema by syringe and catheter.

Groups of rats were killed by decapitation at 15 minutes, 1 hour, 6 hours, 24 hours, 72 hours, and 120 hours. The abdominal and thoracic organs were exposed by a ventral midline incision and were examined grossly. Samples of liver, colon, kidneys, and any other organs showing obvious abnormalities were fixed in buffered 10 per cent formalin or in Zenker's fluid, or in both. The pathologist performed or supervised the gross examination and performed all histologic examinations without knowledge of the group to which the animal belonged or of the type of enema it had received. All sections were stained with hematoxylin and eosin, most colon samples by the mucicarmine method, and selected samples of liver were stained for fat (Oil Red-O) and glycogen (PAS and PAS after diastase digestion).

ONE MINUTE FORCED RETENTION ENEMA STUDIES

A 3.6 ml. quantity of the enema solution was instilled into each rat through a catheter and the enema was forcibly retained in the animal for I minute. At the end of the forced retention period the animal was released and placed in a special observation cage until all animals of that group had been treated. Saline and water control enemas and enemas containing concentrations of tannic acid or clysodrast ranging from 0.1 to 16 per cent were utilized. At the scheduled times of 15 minutes, 1, 6, 24, 72,

^{*} Clysodrast (*) (Barnes-Hind). (4,4' diacetoxydiphenyl)-(pyridyl-2)-methane, 1.5 mg. solubilized with tannic acid, N.F. q.s. 2.5 gm.

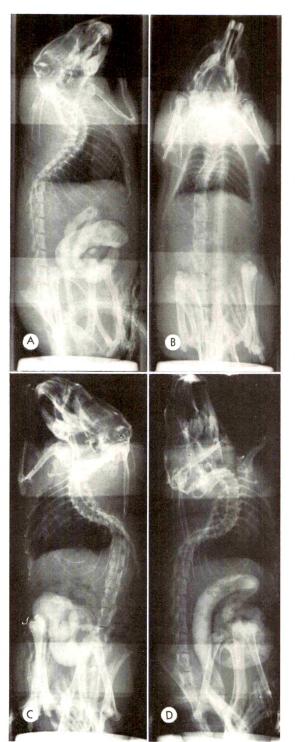


Fig. 2. (A and B) One minute forced retention of barium enema containing 4 per cent tannic acid. (A) Roentgenogram obtained 3 minutes after release. (B) Roentgenogram obtained 20 minutes after release. Note complete emptying. (C and D)

and 120 hours, the assigned animal groups were killed and autopsy performed as described above. Every effort was made to save the animals that died prior to autopsy; however, 3 of these rats were accidentally disposed of and lost to the study.

ONE HOUR FORCED RETENTION ENEMA STUDIES

The case reports of McAlister et al. ⁷ suggest that delayed evacuation of tannic acid containing enemas may have contributed to the fatal outcome. Groups of 3 to 11 rats were studied to determine the effect of prolonged retention of clysodrast in the colon and rectum. Each group received enemas containing concentrations of 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 4.0 per cent tannic acid, respectively. These were held in the colon by closing the anus with a rubbertipped intestinal clamp for I hour. The rats that died had immediate autopsies. The surviving animals were sacrificed at 72 hours and their colons, livers, and kidneys examined. (In the 0.25 to 1 per cent and the 4.0 per cent groups, only the colons and livers were examined.) Three rats received saline enemas by the same schedule.

REPEATED ONE MINUTE FORCED RETENTION ENEMA STUDIES

The effect of repeated tannic acid enemas was studied by giving 3 successive clysodrast enemas at 30 minute intervals to groups of 4 rats each. These enemas contained tannic acid in concentrations of 0.25, 0.75, 1.0, and 2.0 per cent. Each enema solution was retained for 1 minute. The rats were killed 72 hours later and their colons and livers were examined histologically. Four rats received 3 saline enemas in the same manner and were killed and examined 6 hours later.

One hour forced retention of barium enema containing 4 per cent tannic acid. (C) Roentgenogram obtained 15 minutes after release of clamp. (D) Roentgenogram obtained 90 minutes after release of clamp. Note retention.

DEFINITION OF HEPATIC DAMAGE

The histologic alterations in liver samples considered to be significant variations from normal (Fig. 3) were:

- (a) Regenerative change. Although basic architecture was preserved, individual parenchymal cells, usually in central zones of lobules, showed pleomorphism of nuclei. Mitotic activity was markedly increased (Fig. 4) and cytoplasmic outline was sometimes irregular.
- (b) Focal necrosis. Also predominantly central, this change was characterized by coagulative or hyaline necrosis of parenchymal cells. Adjacent cells usually had a high mitotic rate and a slight inflammatory reaction was sometimes present (Fig. 5). When this change occurred, it usually affected multiple lobular units. There was no significant lobar or segmental variation and, when multiple samples of liver were taken, all appeared similar.

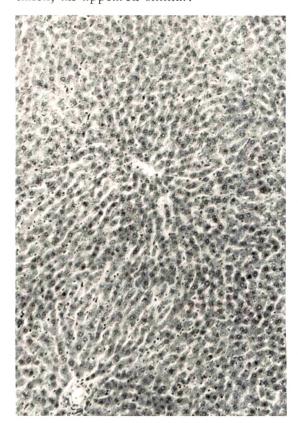


Fig. 3. Section of liver showing normal architecture. From a control rat. (180 ×, H & E.)

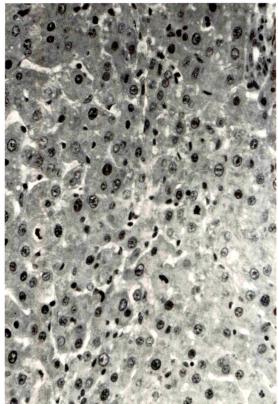


FIG. 4. Regeneration. Liver of rat sacrificed 72 hours after receiving 4 per cent tannic acid in clysodrast. Forced retention 1 hour. Note pleomorphic nuclei, bizarre mitoses, and swollen hepatic cells without other disruption of architecture. (450 ×, H & E.)

(c) Central necrosis. Observed in the animals that died prior to sacrifice and in those animals sacrificed at the 24 and 72 hour periods, this form of necrosis was often confluent. It resembled the pattern produced by other chemical toxic agents and that seen in early fulminant viral hepatitis (Fig. 6).

DEFINITION OF COLONIC CHANGES

The 3 categories of histologic variation from normal (Fig. 7) for the examined colons were:

Edema. This occurred early, was often nonspecific, and was usually resorbed by 72 hours. It consisted of accumulation of protein-rich fluid, predominantly in the submucosa (Fig. 8).

Edema and inflammation. Although it

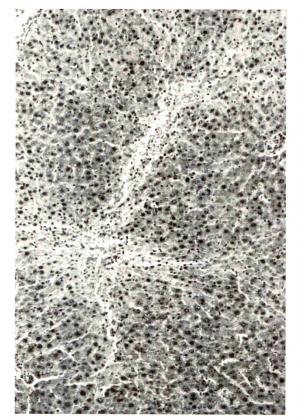


Fig. 5. Focal necrosis. This section of liver is from a rat sacrificed 72 hours after 1 hour forced retention of 4 per cent tannic acid in clysodrast. Necrotic foci are small. Regeneration is also present. (180 ×, H & E.)

could be evoked in controls and by trauma, exudation of fluid and cells (Fig. 9) was generally related to the dose of the test substance. Inflammatory cells were found in the mucosa and submucosa.

Ulceration and hemorrhage. Usually segmentally distributed and grossly visible, this change was observed in the colons of rats which had received tannic acid or clysodrast in the highest concentrations or in which the retention time had been longest. The mucosal surface adjacent to ulcers often had a "tanned" or coagulated appearance. Repair did not occur in 72 hours (Fig. 10).

RESULTS

EFFECT OF GRADED CONCENTRATIONS OF TANNIC ACID OR CLYSODRAST

The results of the first phase of the experimental study, utilizing 270 animals, are

summarized in Table 1. Concentrations up to and including 7 per cent clysodrast or tannic acid produced no hepatonecrosis. Two of 152 animals studied in the 0.1 to 7.0 per cent tannic acid range showed sufficient mitoses to warrant an interpretation of regeneration; however, the possibility of a diurnal surge cannot be excluded. Minor local changes of edema with and without inflammation were seen in the colon. None of these was associated with detectable liver damage. The details of the groups of animals in which the 8 and 16 per cent clysodrast and tannic acid were administered are included in Table 1. One of 15 animals at the 8 per cent level showed evidence of focal necrosis and I evidence of regeneration. In contrast, all of the animals studied at 16 per cent and sacrificed at 24 and 72 hours had evidence of central necrosis or focal necrosis and the colons of these

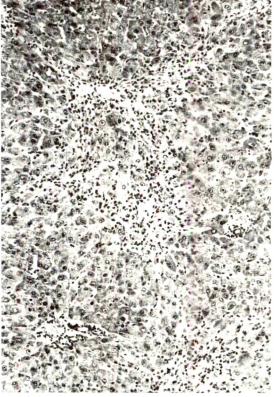


Fig. 6. Central necrosis. More extensive central necrosis in liver of a rat given 16 per cent tannic acid for 1 minute and sacrificed at 72 hours. Note inflammation in necrotic central zones and regeneration in viable cells. (180 ×, H & E.)

animals were ulcerated and hemorrhagic. Six of the 16 rats scheduled for sacrifice at 24 and 72 hours died prior to those times.

EFFECT OF ONE HOUR FORCED RETENTION OF ENEMAS

A sixtyfold increase in the minimum ex posure to intracolonic solutions of clysodrast resulted in hepatic necrosis in 10 of 12 rats receiving 3.0 or 4.0 per cent concentrations (Table II). Two of the animals of the latter group died. Changes in the colon also resembled those seen in animals given 16 per cent solutions for 1 minute. One of the 6 animals given 2.5 per cent clysodrast also had focal necrosis of the liver. The kidneys that were examined histologically were normal.

EFFECT OF 3 REPEATED ONE MINUTE RETENTION ENEMAS

This method with clysodrast concentrations of 0.25 to 2.0 per cent was used in 16 animals; 4 controls received saline. At the 1 and 2 per cent levels, livers of 2 rats

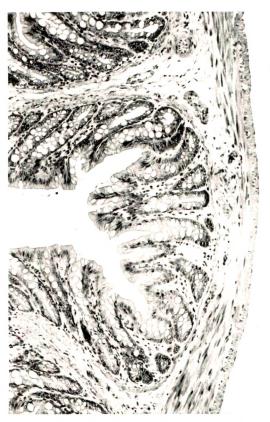


Fig. 7. Normal colon of a rat. (180 ×, H & E.)



Fig. 8. Edema of mucosa and submucosa of colon of a rat given 6 per cent tannic acid in clysodrast enema for 1 minute, sacrificed at 6 hours, There is very little inflammation. Note massive widening of submucosa. Mucous vacuoles are reduced in size and number. (180 ×, H & E.)

showed slight increase in parenchymal cell mitoses. This finding was considered insufficient to meet the definition of regenerative change employed in this study. It was, however, denoted as a \pm change (Table III). No other changes were noted in the colons or livers examined at 72 hours.

DISCUSSION

Four major factors are postulated to explain intra-group variations in lethal effect or morphologically demonstrable hepatic or colonic damage. These are: (1) variations in susceptibility; (2) variations in effective retention time of the enema; (3) variation in distribution of the enema solution within the colon (due to feces); and (4) sampling error inherent in the selection of tissues for microscopic examination.



Fig. 9. Edema and inflammation of colon of rat sacrificed 6 hours after a 1 minute 16 per cent tannic acid enema. All coats are inflamed. Mucosal surface shows coagulative necrosis. (180 ×, H & E.)

INTERPRETATION OF HEPATIC CHANGES

The primary purpose of this study was toxicologic, not histologic. The "end point" was severe and often lethal hepatic necrosis. The use of tannic acid as a method to produce more subtle changes at the cellular level has been described in a serial electron micrographic study of rabbit livers by Arhelger, Broom, and Boler who observed glycogen decrease in I hour and submicroscopic fatty change as early as 4 hours after subcutaneous injection of tannic acid at a single administered dose equivalent to 800 to 1,333 mg. per kilogram. No lower dose levels were reported.

Focal necrosis and central or confluent necrosis were obvious. The changes resembled those described in failure of human livers after tannic acid treatment of burns and those in experimentally induced tannic acid necrosis. Central necrosis produced by

this "open" enema method was less massive than that produced by "closed" intraperitoneal administration.4 With lower doses of tannic acid or clysodrast, the necrotic changes became more subtle. In some animals with such low doses, it was impossible by light microscopy to distinguish centrolobular vacuolization from normal variations. In none of these previously healthy rats on standard diet were advanced fatty changes, as described in some fatal human cases,7 observed. This is in accord with earlier experimental studies.^{2,5} Fat was not seen in significant quantities in normal livers or in those showing slight focal necrosis or regeneration. Fat vacuoles were observed at the margins of zones of extensive central necrosis. Large hydropic vacuolated cells, usually concentrated about central veins, also did not contain significant quantities of glycogen when evaluated by the periodic acid-

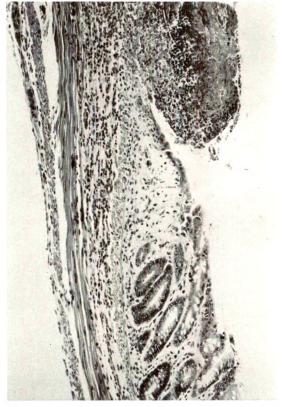


Fig. 10. Ulcer with hemorrhage of mucosa of colon of rat given 4 per cent tannic acid in clysodrast for 1 hour, sacrificed at 72 hours. (180 ×, H & E.)

Table I

One minute forced retention studies

HISTOPATHOLOGIC OBSERVATIONS ON LIVERS AND COLONS OF RATS GIVEN 3.6 CC. ENEMAS CONTAINING VARIOUS CONCENTRATIONS OF CLYSODRAST AND TANNIC ACID

Time				Hepatic	: Change	S		Change	es in Colo	n
Sacrifice; Immediate Necropsy	Concentrations of Clysodrast and Tannic Acid	No. of Animals	None	Regen- eration	Focal Necro- sis	Central Necro- sís	No. of Colons Sec- tioned	None	Edema and Inflam- mation*	Ulcera- tion and Hemor- rhage*
(Hours)	Controls (noth-									
I to 72	ing; saline; water)	42	42			sou announce de l'article de l'	42	40	2	
1/4 to 72	Clysodrast 1 to	152	150	2	O PROGRAMMA CONTRACTOR		113	90	22	Ι±
1 to 72	Tannic acid 1 to 7%	36	36			derettelmilde und der der der der	25	15	10	
6	Clysodrast 8%	4	4				4	1	2+ 1++	
24	Clysodrast 8%	4	3		1ª		4	3	1b	Control
72	Clysodrast 8%	4	4				4	4	vocation of the contract of th	
120	Clysodrast 8%	4 (1†)	2	I				not control to the co		
6	Clysodrast 16%	4	4				4		4	
6	Tannic acid 16%		2	2			4		4	
24	Clysodrast 16%	4			1	3°	4		•	4
		(3‡)								
24	Tannic acid 16%	4 (2‡)			3 ^d		4		A CONTRACTOR OF THE CONTRACTOR	4
72	Clysodrast 16%	4			4					
72	Tannic acid 16%	4			I	2			**	
		(1†)							4 and the second	

* Plus and plus-and-minus marks denote degree of edema.

† Number of animals dying prior to sacrifice not available for necropsy.

‡ Number of animals dying prior to sacrifice on which necropsies were performed.

a=Also had liver granuloma. b=Also had serosal granuloma. c=3 which died. d=2 of these died.

Schiff reaction, with and without diastase digestion.

Individual cell necrosis and mitotic activity were frequently seen together and somewhat arbitrarily designated "regeneration." The capacity of hepatic parenchyma to restore itself after partial ablation or toxic damage is known to be remarkably rapid. For this study, striking regenerative activity was interpreted as the lowest grade on our scale of damage, although at 72 hours it may have represented the recovery phase from more severe damage. Normal livers rarely showed a single parenchymal mitosis in 10 high power microscopic fields. Counts of 5 to 10 mitoses per high power

field were interpreted as evidence of regenerative change.

INTERPRETATION OF CHANGES IN THE COLON

The alterations in the colon were proportional to the dose level of tannic acid or clysodrast. Rare instances of catheter erosion and 2 perforations were exceptions, and, of course, alterations varied with the time of sacrifice. For purposes of grading, the changes were listed as (1) edema; (2) edema and inflammation, and (3) ulceration and hemorrhage. The first 2 categories cover the simple inflammatory response elicited by any number of agents or by mechanical trauma. These reactions were

TABLE II

ONE HOUR RETENTION STUDIES

HISTOPATHOLOGIC OBSERVATIONS ON LIVERS AND COLONS OF RATS GIVEN 3.6 CC. ENEMAS CONTAINING VARIOUS CONCENTRATIONS OF CLYSODRAST (NECROPSIES AT 72 HOURS)

6			Hepat	ic Change	3	Changes in Colon					
Concentra- tions of Clysodrast	No. of Animals	None	Regen- eration	Focal Necrosis	Central Necrosis	None	Edema	Edema and Inflamma- tion	Ulceration and Hemor- rhage		
Saline (controls) 0.25 and	3						A CONTRACTOR OF THE CONTRACTOR				
0.5%	11	11				11	To a management of the state of				
$^{1}\%_{1.5\%}$	3 5	3 5		and the second		3 5					
2.0%	6*	5	Landar Landar Paris			5					
2.5% 3.0%	6* 6	4	T	I		5					
4.0%	6**	1		2	3**	1	1		3†		

^{*} I rat died, not available for necropsy.

TABLE III

ONE MINUTE FORCED RETENTION STUDIES, REPEATED THREE TIMES, EVERY 30 MINUTES HISTOPATHOLOGIC OBSERVATIONS ON LIVERS AND COLONS OF RATS GIVEN 3.6 CC. ENEMAS CONTAINING VARIOUS CONCENTRATIONS OF CLYSODRAST (NECROPSIES AT 72 HOURS)

			Не	epatic Chang	ges	Ch	Changes im Colon				
Concentrations of Clysodrast	No. of Animals	None	Regenera- tion	Focal Necrosis	Central Necrosis	None	Edema and Inflamma- tion*	Ulceration and Hem- orrhage			
Saline†	4					2	1+,1++	accompany group and to one or security and			
0.25%	4	4				4 C 4 T 4 D					
0.75%	4	4				4 C 4 T 4 D		-			
1.0%	4	3	1+			4 G 4 T 4 D					
2.0%	4	3	1+	Management of the Control of the Con		4 C 4 T 4 D		-			

^{*} Degree of edema indicated by plus marks.

^{** 2} rats died, necropsy performed.

^{† 1} of 3 rats died, necropsy performed.

[†] Necropsies at 6 hours.
C = cecum; T = transverse colon; D = descending colon.

usually focally distributed and rarely observed grossly. Chance in selection of samples was an important factor in their detection.

Severe inflammations with crypt abscesses, ulcers, mucosal hemorrhages, and coagulative mucosal necrosis were considered direct corrosive effects of tannic acid. In this sense, the high concentrations of tannic acid in pure solution or in clysodrast were "toxic." These effects could be distinctly separated from the nonspecific transient reactions to saline, water, and low concentrations (0.25 to 2.0 per cent) of tannic acid. Within the limit of the number of samples examined, advanced changes in the colon were associated, almost invariably, with hepatic necrosis. Unlike the minor reversible changes caused by low concentrations, the toxic levels produced such extensive damage to the colon that it was not repaired in 72 hours (Fig. 6).

SUMMARY

- 1. Based on the 1 minute forced retention studies, the lowest concentration of a tannic acid or clysodrast containing enema producing liver necrosis was 8 per cent. Based on the extreme condition of a forced 1 hour retention enema, liver damage was detected at the 2.5 per cent level.
- 2. Colonic "damage" exceeding the resorbable edema and minor inflammation observed in some controls again was a function of dose and contact time. Coagulative necrosis and hemorrhage of colonic tissue, persisting for 72 hours, were seen after 16 per cent tannic acid or clysodrast containing 1 minute enemas and 4 per cent clysodrast containing enemas forcefully retained for 1 hour. Under this condition, liver damage was almost invariably associated with these alterations in colonic mucosa. At the highest levels death occurred in 8 of 22 animals prior to the 24 and 72 hour times of scheduled sacrifice.
- 3. At the concentrations (0.25 per cent to 2.0 per cent) employed, 3 consecutive I

minute retention enemas given at half-hour intervals did not produce liver damage in animals sacrificed at 72 hours.

4. There was no detectable difference between the colonic or hepatotoxic effects of clysodrast and tannic acid.

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TOXICITY STUDIES ON TANNIC ACID ADMINISTERED BY ENEMA*

II. THE COLONIC ABSORPTION AND INTRAPERITONEAL TOXICITY OF TANNIC ACID AND ITS HYDROLYTIC PRODUCTS IN RATS

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ANNIC acid has been proposed to be a hepatotoxic agent which under rare instances has led to death in humans after the administration in enemas used in preparation for roentgenologic examination or after incorporation in the barium enema. Since gastrointestinal absorption must have preceded hepatotoxicity, the conditions necessary for absorption are of interest. Unfortunately, absorption from the gastrointestinal tract has been poorly defined, largely due to the lack of adequate methods to detect intact tannic acid in biologic fluids and to distinguish it from the hydrolysis products, gallic acid, and related polyhydroxy acids. The effects of the route of administration, diet, or species and strain variability have not been established.

The chemistry of (gallo-) tannic acid is well known.⁷ Although it is probably of heterogenous composition, there is no doubt that it is a large, complex glucosidic polyester of gallic acid and related phenolic acids. The molecular weight has been proposed to be in the range of 1,500 to 2,000. It reacts to form precipitates with proteins, mucoproteins, alkaloids, and various cationic compounds. Further, being an ester, the compound is labile to hydrolysis in moderately alkaline solutions and also very easily hydrolyzed by esterases.^{7,8}

The nature of the toxic response to tannic acid is central lobular hepatonecrosis, regardless of the method of administration. However, the conditions under which the toxicity occurs are not clear. The nature of

the toxicity was first widely recognized in connection with the use of tannic acid in burn therapy.^{1,2,4,15,16}

Tannic acid given in the diet in 1 and 2 per cent concentrations for 3 months has shown no hepatonecrosis in rats. 6 When mice were given 10 per cent solutions of tannic acid by stomach tube, the LD50 obtained was between 3,000 and 4,000 mg./kg.14 However, no histopathologic data were obtained and it is not known precisely what caused their death in this study. Toxicity by the oral route has been demonstrated in rats, dogs, and rabbits9 with solutions of tannic acid in concentrations of 2.5, 5, and 10 per cent. However, other investigators3 were unable to demonstrate hepatonecrosis from orally administered tannic acid in daily doses of 50 mg./kg. to 1,000 mg./kg. given to white male Wistar rats over many weeks. Still another study was conducted to determine the oral toxicity in rabbits5,12 of tannic acid isolated from Ouercus havardi and shin oak. In this instance, the LD50 was determined but, again, histologic evidence was not reported. Tannic acid from the oak was toxic when given orally as evidenced by death and gross descriptions of various organs. Some evidence of hepatonecrosis has been obtained when tannic acid was given as a 5 per cent solution in a barium enema to dogs.10

Korpássy and co-workers⁹ and Blumenberg and co-workers³ administered tannic acid to rats by way of stomach tubes. The

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former group demonstrated hepatotoxicity in their studies while the latter apparently found none. Blumenberg et al. used white male Wistar rats while Korpássy et al. did not state the strain of rats that were used. Also, the time during the day of administration of the tannic acid may be very important since rats are nocturnal animals. The food content of the stomach and intestines would, no doubt, influence the total absorption of tannic acid, its rate of absorption, and probably the degree of hydrolysis to gallic acid within the gastrointestinal tract. In addition, the type of diet used by these investigators differed widely. Blumenberg et al. used a standard diet and Korpássy *et al.* used waste food.

Methods of assaying for tannic acid in the blood have included ferric ion and arseno-tungstic acid colorimetric procedures and chromatographic estimations. Cameron and co-workers4 and McAlister and co-workers10 used the ferric ion complex to construct blood level curves of tannic acid, while Korpássy and co-workers used the arseno-tungstic acid procedure. Neither of these assays are specific for tannic acid, as most free phenolic-like compounds yield the same color which is measured spectrophotometrically. Hence, the hydrolysis product of tannic acid, which is predominantly gallic acid, will give a color in these assays which is impossible to differentiate from tannic acid. It has also been shown conclusively8 that tannic acid is broken down in the gastrointestinal tract to gallic acid and other substances at an appreciable rate. Therefore, it is not correct to use these colorimetric procedures and to claim that the positive values obtained confirm the absorption of intact tannic acid.

Preliminary investigation of the method used by Blumenberg et al. of extraction and chromatography of the blood samples containing known amounts of tannic acid produced ambiguous results in our hands and lacked sensitivity. A new method of thin layer chromatographic detection of tannic acid and gallic acid directly from the serum was therefore utilized.¹¹

Two studies were undertaken to further define the specific conditions for tannic acid toxicity and for its colonic absorption. The first was designed to demonstrate the characteristic histologic damage produced by tannic acid, as opposed to that produced by gallic acid when these compounds are administered by intraperitoneal injection into rats. The second study was undertaken to determine if intact tannic acid could be obtained from the hepatic portal vein during the administration of a tannic acid enema to rats and to attempt to specify the concentration and time factors involved in the absorption of intact tannic acid.

MATERIALS AND METHODS

INTRAPERITONEAL STUDIES

Tannic acid, N.F., clysodrast* and gallic acid were administered by peritoneal injection into groups of 5 Long-Evans female rats weighing between 130 and 170 gm. The concentrations of all injections were adiusted so that the volume administered was between 0.8 and 1.2 ml. and the pH of all solutions or suspensions was between 2 and 3. The amount given was adjusted according to the weight of the rat so that a constant dose per kilogram was administered. All doses of tannic acid administered were solutions. The two highest doses of gallic acid exceeded the solubility of the compound in water and were prepared as suspensions in sterile 2 per cent carboxymethylcellulose, medium viscosity grade. The dosages of tannic acid and clysodrast were: 5 mg./kg., 20 mg./kg., 40 mg./kg., 60 mg./kg., and 80 mg./kg. The gallic acid dosage was: 80 mg./kg., 100 mg./kg., 120 mg./kg., 150 mg./kg., 1,000 mg./kg., and 2,000 mg./kg.

The rats were sacrificed by decapitation in 48 hours, and liver, kidney, and colon tissue samples were obtained and fixed immediately in Zenker's solution. Hematoxylin-eosin stained slides were prepared of the tissue samples so obtained. The

^{*} Clysodrast (Barnes-Hind). (4,4'-diacetoxydiphenyl)-(pyridyl-2)-methane, 1.5 mg. solubilized with tannic acid, N.F. q.s. 2.5 gm.

pathologist who interpreted the slides was uninformed of the identity of each group and had read all the slides in the colonic enema study reported in Part 1 of this series. The series and 80 mg./kg. tannic acid groups and one in the 80 mg./kg. clysodrast group before the scheduled time of sacrifice. These were examined at necropsy, approximately 1 hour after death. Four rats died in the 2,000 mg./kg. gallic acid group. Necropsies were performed on all shortly after death.

COLONIC ABSORPTION STUDIES

Long-Evans female rats, weighing between 200 and 250 gm., were anesthetized with sodium pentobarbital by administering 40 mg./kg. intramuscularly into the thigh. An enema of appropriate concentration, consisting of 3.6 ml. of tannic or gallic acid, was forcibly retained in the colon for I minute in 20 animals. Following this, the anus was unclamped and the animals were allowed to expel freely. However, from the previous study¹³ it is known that considerable volume of the enema was retained in the animal for 10 to 30 minutes after removal of the clamp. In 3 animals the clamp was maintained on the anus for 15 minutes and in 3 others for 1 hour in order to study the effect of tannic acid retention for a longer period of time. Portal blood samples were obtained at the end of these 3 retention periods. Portal blood was collected because it was assumed that the tannic acid would be bound by the liver tissue and not be detectable in the blood from the central compartment. In 3 rats, blood was taken from the thoracic inferior vena cava at the end of I minute or 15 minute retention times.

After giving the enemas, a midline incision was made and the portal vein was exposed. A 25 gauge needle connected to a 5 ml. syringe was used to withdraw the blood. Approximately 5 to 8 minutes were required to prepare the animal for blood collection and an additional 5 minutes were necessary to withdraw 2 to 3 ml. of blood. Only one sample was obtained per rat. All

blood samples were centrifuged immediately; the serum was separated, appropriately coded, and refrigerated. The chromatography was performed within 24 hours.

Twenty microliter aliquots of the serum were applied to Silica Gel G chromatography plates. The plates were first developed with chloroform and then were re-developed with ethyl acetate-formic acid, 8:2. The RF of the gallic acid was found to be 0.9 with a detectability of 0.2 micrograms (μ g.) and that of the tannic acid was 0.7 to 0.8 with a detectability of 0.5 μ g. In each day's determination, one control serum sample from an animal administered a 16 per cent tannic acid enema was labeled as such, and results were obtained from each test series before the code was broken. Known concentrations of tannic acid and gallic acid were run with each chromatographic plate. Each sample was run in duplicate.

RESULTS AND DISCUSSION INTRAPERITONEAL STUDIES

Table 1 is a summary of the findings from histologic examination of the necropsy specimens obtained from the intraperitoneal toxicity study. It is to be noted that the intraperitoneal injection of 5, 20, and 40 mg./kg. doses of the tannic acid or the clysodrast did not produce observable liver damage or other tissue damage. The 60 and 80 mg./kg. dose of both tannic acid groups produced classic liver damage, varying from minimal change to massive central lobular necrosis. None of the animals showed any evidence of renal or colon damage. The 3 animals which died before the scheduled sacrifice time showed similar findings and no distinguishing characteristics.

The intraperitoneal injection of an 80, 100, 120, 150 mg./kg., or 1,000 mg./kg. dose of gallic acid did not produce histologic liver damage nor grossly observable tissue damage to other organs. The 2,000 mg./kg. dose of gallic acid produced renal damage varying from no or minimal changes to extensive changes characterized

 $T_{\rm ABLE~I}$ Intraperitoneal toxicity studies of tannic acid, clysodrast, and gallic acid in rats

		Hepatic	Changes			Renal	Changes	
Drug and Dose Level	Normal	Regener- ation	Focal Necrosis	Massive Necrosis	Normal	Interstitial Hemor- rhage	Tubular Dilatation	Tubular Epithelial Necrosis
Tannic Acid	AV-1		**************************************	eren er er en		***************************************	2754 VINNARY (1884	
5 mg./kg.	5				I			
20 mg./kg.	5				I			
40 mg./kg.	5				I			
60 mg./kg.		3	2		1			
80 mg./kg.			3	2	1			
Clysodrast								
5 mg./kg.	5				1			
20 mg./kg.	5				1			
40 mg./kg.	5				1			
60 mg./kg.		3	2		1			
80 mg./kg.		3		2	I			
Gallic Acid								
80 mg./kg.	5				1			
100 mg./kg.	5				I			
120 mg./kg.	5				I			
150 mg./kg.	5				1			
1,000 mg./kg.	5				1			
2,000 mg./kg.	5				I	4*	4*	4*

All colons were normal.

The kidneys were grossly inspected at the time of sacrifice. Random samples were taken from each test group. In the group given gallic acid, 2,000 mg./kg, there were gross renal changes. Therefore, all kidneys were examined.

* All types of renal damage were seen in each animal.

by hemorrhagic kidneys with extreme tubular dilatation, epithelial necrosis and proteinaceous casts. Four of the 5 rats died at the 2,000 mg./kg. level. They died secondary to renal damage including hemorrhage and tubular epithelial necrosis. The rats at this dosage level did not show any significant hepatic changes other than those attributable to autolysis or imperfect fixation. There was no evidence of hepatic necrosis in any animal administered gallic acid.

From our studies on the toxic response to intraperitoneal injections, it is clear that relatively large amounts of tannic acid must be absorbed in order to elicit a hepatotoxic effect. In the usual toxicologic procedures, a lethal dose—50 per cent (LD50)—is taken as the dose required to kill 50 per cent of the test animals under the test

conditions. It is to be noted that the data in Table 1 on the intraperitoneal studies can be used to establish a hepatotoxic dose—50 per cent (HD₅₀)—using as the criterion of toxicity the definition of liver damage specified in Part 1 in this series. 18 The 40 mg./kg. dose produced no detectable hepatotoxic change (HD₀), while the 80 mg./kg. dose produced focal or massive necrosis in all of the animals administered tannic acid, and in 2 of 5 administered clysodrast. With both drugs, the 60 mg./kg. dose produced focal necrosis in 2 animals and regeneration in 3 animals. Therefore, we propose that the HD₅₀ is in the region of 50 mg./kg. tannic acid or clysodrast for this species.

In comparison, instillation of single dose enemas as reported earlier¹³ produced hepatonecrosis in 1 of 16 animals administered an 8 per cent enema forcibly retained 1

minute. The 16 per cent 1 minute forced retention enemas (570 mg. total tannic acid administered) caused focal necrosis or massive necrosis in all the animals sacrificed at 24 or 72 hours. The liver specimens from the 16 per cent enemas were similar histologically to those seen in the animals administered intraperitoneal tannic acid at dose levels of 60 mg./kg. and 80 mg./kg.

COLONIC ABSORPTION STUDIES

The lowest level of detectability established by the thin layer chromatographic procedure was 0.5 μ g. for tannic acid and 0.2 μ g. for gallic acid in the blood sera. The size of the spots and the intensity of color were compared with control standards ranging from 0.5 to 2.5 μ g. for tannic acid and 0.2 to 1.0 μ g. for gallic acid, in order to obtain a rough assessment of the level of the compounds in each sample. Unfortu-

nately, we were unable to differentiate these easily and arbitrarily divided them into 3 levels, namely +1 to +3. In one instance a blood sample produced variable results during repeated studies and, possibly, contained more than 2.5 µg. of tannic acid. This was designated as +2 to +4 (Table II).

In the 1 minute forced retention study, we were unable to detect tannic acid from the serum samples of animals administered 0.5, 1, and 1.5 per cent tannic acid enemas. In the 2.0, 2.5, and 3.0 per cent enemas, tannic acid was noted at the limit of detectability of the method. This was designated as +1. The sera samples from animals receiving 4 per cent and 16 per cent tannic acid enemas contained higher concentrations of detectable tannic acid; however, tannic acid recovery from the sera of animals administered 16 per cent varied from

Table II
ABSORPTION OF TANNIC ACID AND GALLIC ACID IN ENEMAS ADMINISTERED TO RATS

Concentration in Enema	No. of Animals	Forced Retention Time	Source of Blood Sample	Tannic Acid*	Gallic Acid*
Tannic Acid	- 19 <u>19 19 19 19 19 19 19 19 19 19 19 19 19 1</u>				
16.0%	4	1 min.	Hepatic portal vein	+1 to +3	+2 to +3
4.0%	Ī	I min.	Hepatic portal vein	+2	+2
3.0%	I	I min.	Hepatic portal vein	+	+
2.5%	2	1 min.	Hepatic portal vein	+	+
2.0%	2	I min.	Hepatic portal vein	+ (?)	+
1.5%	4	I min.	Hepatic portal vein	0	+
1.0%	2	I min.	Hepatic portal vein	0	0
0.5%	1	I min.	Hepatic portal vein	0	0
16.0%	2	1 min.	Thoracic inferior vena cava	0	+
0.25%	I	15 min.	Hepatic portal vein	0	0
0.25%	1	ı hr.	Hepatic portal vein	0	0
1.0%	I	15 min.	Hepatic portal vein	0	+
1.0%	Ţ	ī hr.	Hepatic portal vein	0	+
2.0%	I	15 min.	Hepatic portal vein	++	++
2.0%	I	ı hr.	Hepatic portal vein	+2 to +4	+3
16.0%	I	15 min.	Thoracic inferior vena cava	++	+3
Gallic Acid					
4.0%	I	т min.	Hepatic portal vein	0	+5
2.0%	I	1 min.	Hepatic portal vein	0	+3
1.0%	I	1 min.	Hepatic portal vein	0	++

^{*} The above designation of + values is used to indicate relative concentration. These were roughly estimated by: (a) the known limit of detectability of each compound; (b) the rough evaluation of the 16 per cent enema spots against controls (which varied from day to day); and (c) the intensity of color and size of the individual spot. It is likely that the estimated level of drug may vary as much as 100 per cent of the true value. The estimates of gallic acid at the lower levels were complicated in several instances where the serums contained hemoglobin from lysed red blood cells.

• **e**

sample to sample. By comparison with the controls they were designated as +1 to +3. Similarly, the gallic acid spots varied from +1 to +3, as noted in Table 11.

Even after 15 minutes or 1 hour forced retention, no intact tannic acid was detectable from the sera obtained after 0.25 per cent and 1.0 per cent tannic acid enemas. The serum from animals given a 2.0 per cent tannic acid enema, forcibly retained for 15 minutes and 1 hour, contained a level of tannic acid somewhat above the minimum detectable level. It was not possible to define these levels quantitatively.

It is important to note that the chromatographic method was able to establish the absence of tannic acid in all control animals and animals given gallic acid enemas.

The results suggest that the amount and degree of absorption are concentration and time dependent. Serum tannic acid was not detected after administration of enemas containing up to I per cent, even if retained for 1 hour. Since 3.6 ml. of the tannic acid solution was instilled, this means that 72,000 μ g. was administered in the enema. The level of detection for tannic acid by the chromatographic procedure is 0.5 μ g./20 μ l. of applied sera or 25 μ g./ml. of plasma. Two to 3 ml. of whole blood from the hepatic portal vein was obtained during a period of 5 minutes, and, therefore, approximately 75 μg. out of a total of 72,000 μg. administered was detected. Assuming that sufficient solution is retained for absorption to continue for 30 minutes, this might result in as much as 0.5 mg. being absorbed from the single dose. This could be as much as 100 per cent in error due to technical and animal variations.

Gallic acid, a hydrolytic product of tannic acid, was detected in the serum samples obtained from the thoracic inferior vena cava in 3 animals administered a 16 per cent tannic acid enema. In 2 of these animals, the enema was retained for 1 minute and in 1 it was retained for 15 minutes. In contrast, no intact tannic acid was found in the sera from the thoracic inferior vena

cava in these animals except when the 16 per cent tannic acid enema was forcibly retained for 15 minutes. These data further emphasize the likelihood that the earlier methods utilized to detect tannic acid in the blood probably resulted in the detection of the hydrolytic products and not intact tannic acid.

SUMMARY

- 1. After intraperitoneal administration of tannic acid to rats, the dose sufficient to cause hepatotoxicity in 50 per cent of the animals (HD_{50}) is in the region of 50 mg./kg.; the HD_{0} is 40 mg./kg.
- 2. After intraperitoneal injection, gallic acid produces no hepatotoxic response, even at lethal levels. The cause of death in these cases is due to renal damage.
- 3. Tannic acid could not be detected in the portal vein blood samples after instillation of 1 per cent tannic acid enemas even though retained for 1 hour. Minute amounts of tannic acid were detected in the portal vein blood samples after instillation of 2 per cent tannic acid enemas forcibly retained for 1 minute.
- 4. Increased concentration of tannic acid in the enema and a longer period of colonic exposure result in increased amounts of intact tannic acid being detected in the portal venous blood.
- 5. Although intact tannic acid could be detected in blood samples from the thoracic inferior vena cava following a 16 per cent tannic acid enema maintained in the colon for 15 minutes, it could not be detected when the enema was maintained for 1 minute. In contrast, gallic acid could be detected at both time periods. This suggests that the nonspecific methods utilized to detect tannic acid in the blood, as reported previously, resulted in the detection of gallic acid rather than of tannic acid.

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intact tannic acid from subsequent tannic acid containing enemas. They further stated that all these patients evacuated the tannic acid enema poorly.

Lucke et al.3 used 2 per cent tannic acid in the barium sulfate enema. On the basis of the animal data now at hand, such dose level, if retained sufficiently long, may be toxic per se. Particularly is this true in a colon that may have been previously injured by preparatory cleansing efforts. McAlister's group used a dose of 0.75 per cent tannic acid, repeated in all 3 patients. Whereas a single dose of 0.75 per cent tannic acid was probably not hazardous, it may have become so when used repeatedly, particularly after the multiple preliminary saline enemas.

Interacting variables must be considered as having contributed to these unfortunate results. They are: tannic acid concentration in the enema, length of time that the tannic acid was in contact with the colonic mucosa, possible previous colonic damage from cleansing agents, and weight of the patient in relation to dose.

From the experiments conducted on rats, the usual doses of tannic acid appear to have a large margin of safety. The clinical use of multiple cleansing enemas or repeated administration of irritating oral cathartics, which might lead to colonic damage, could narrow this safety factor. Repetition of the tannic acid enema or retention of large amounts of its contents may also affect this margin of safety. It could be further reduced in patients suffering from ulcerative diseases of the colon or from parenchymal diseases of the liver.

There is no proof, however, that a tannic acid enema in a concentration of 0.25 or 0.5 per cent has ever produced hepatotoxicity.

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LIVER FUNCTION STUDIES IN PATIENTS RECEIVING ENEMAS CONTAINING TANNIC ACID*

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CINCE 1946,11 tannic acid has been O widely used in barium enema examinations for cleansing and mucosal delineation. Thomas,²² in 1963, estimated that, annually, 600,000 patients receive enemas containing tannic acid. This practice was surprising since no scientific work had yet established safe, effective dose levels of tannic acid. Radiologists were aware that the correct amount of tannic acid in the enema was important, since weak solutions were not efficacious and strong solutions were known to cause cramps. Not until 1963, however, was fatal liver damage reported in patients who had received barium enemas containing tannic acid.

McAlister et al.¹⁴ reported deaths in 3 children, each of whom had received enemas containing 0.75 per cent tannic acid. In each instance, 2 or 3 enemas had been given on the same morning. Lucke, Hodge, and Patt¹³ reported fatalities in 5 patients subsequent to barium enemas containing 2 per cent tannic acid. In the latter group, 3 adults received an additional 0.25 per cent of tannic acid in the form of clysodrast* in the cleansing enema. Tannic acid was considered as having been the potential hepatotoxin in both of these reports.

To our knowledge, no severe reactions or deaths have been reported when tannic acid was used in a solution of 1 per cent or less in a single examination. Steinbach and Burhenne²¹ reported their clinical experience with the use of tannic acid in a con-

centration of 0.8 to 1.0 per cent. The present study is an attempt to determine whether tannic acid administered by enema in this dose range produces subclinical liver damage. For this purpose, the most sensitive tests of liver function were employed.

MATERIAL AND METHOD

Tannic acid was used for both the cleansing and the diagnostic enemas in 45 patients referred to the Department of Radiology for barium enema examinations. These patients were between the ages of 5 months and 82 years. An additional 10 patients, 2 to 65 years of age, were given enemas without tannic acid, and served as a control group.

Excluded from this study were only those patients in whom gross bleeding or active ulcerative colitis was present. Those with cirrhosis, jaundice, metastatic liver involvement, or other known liver damage were included.

All patients were similarly prepared for the barium enema examination, *i.e.*, castor oil and a water enema were administered on the evening preceding the roentgen study. Both a cleansing enema and a barium enema were given on the same morning in the Department of Radiology. The patients were divided into 3 groups (Table 1).

Group I. Ten patients served as controls and received no tannic acid. A tap-water cleansing enema of 1,000 cc. preceded the routine barium enema examination. These patients were alternated with those in Group II.

^{*} Clysodrast® Barnes-Hind Lot 113663. Clysodrast is a combination of 1.5 mg. of 4,4'-diacetoxydiphenyl-(pyridyl-2)-methane with 2.5 gm. tannic acid to increase its solubility.

^{*} Presented at the Sixty-fifth Annual Meeting of the American Roentgen Ray Society, Minneapolis, Minneapola, September 29-October 2, 1964.

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Group II. Ten patients each received cleansing enemas of I liter of water mixed with 2.5 gm. of clysodrast. A barium enema with the same concentration of clysodrast followed immediately. Thus, each enema contained 0.25 per cent tannic acid.

Group III. Thirty-five consecutive patients received a clysodrast cleansing enema containing tannic acid in a concentration of 0.25 per cent. The subsequent routine barium enema contained a 0.5 per cent concentration of tannic acid.†

All 55 patients underwent liver function tests immediately before administration of the cleansing and barium enemas. These studies were repeated at 24 hours in all patients. Repetition at this interval was considered reasonable since 5 of the 8 fatalities reported^{13,14} had occurred within 72 hours after enemas containing tannic acid had been administered. Moreover, in animal experiments, changes in liver function within 24 hours after administration of tannic acid had also been reported.2,6 As an added control, the last 15 patients in Group III underwent liver profile studies at 3 and 7 days. Each of the liver profile examinations consisted of: (1) direct serum bilirubin;^{4,15} (2) total serum bilirubin;^{4,15} (3) serum glutamic pyruvic transaminase;17,18 (4) lactic acid dehydrogenase levels;23 and (5) lactic dehydrogenase isoenzyme patterns.7,8,23

The cleansing enema consisted of I liter of fluid. For the barium enema examination, 2 liters of the barium solution were prepared. The exact amount administered and the estimated amount expelled were recorded. When poor evacuation or considerable small bowel reflux was noted, roentgenograms of the abdomen were repeated in 24 hours to assess the amount of barium retained. The time from beginning of the colon examination to expulsion of the enema in the toilet did not exceed 30 minutes in any patient.

Since measurement of powder by spoon was considered grossly inaccurate, the tan-

nic acid was used in a solution and measured with a graded syringe.

RESULTS

Only 1 of the 45 patients receiving tannic acid containing enemas showed an abnormal elevation of any of the indicators of liver function (Table 1). The total bilirubin value in this patient (Case 26) increased from 0.7 mg. per cent to 1.3 mg. per cent. The more sensitive indicators of liver function, however, remained normal. Cleansing and barium enemas with tannic acid were repeated 5 weeks later. Liver profile studies before and 24 hours after the second examination were entirely normal.

When indicators of liver function were abnormally high before tannic acid enemas in patients with known or suspected liver disease, the profile values decreased rather than increased after subsequent enemas. This decrease can probably best be explained by the bed rest and hospital care after admission.

One patient, Case 32 (Group III), underwent a liver biopsy 24 hours after the tannic acid containing enemas. Nessler's reagent, as reported by Cameron, Milton, and Allen³ and McAlister *et al.*,¹⁴ was applied to fresh tissue. The reaction for tannic acid was negative, indicating its absence. Histologic examination revealed the liver tissue to be normal.

DISCUSSION

Medical reports implicating tannic acid in enemas as the causative agent for fulminating hepatic necrosis appeared in 1963. 14,22 Reconsideration of its use in enemas has been strongly recommended. 9,11 Abandonment of tannic acid on clinical grounds appeared imminent without, however, insistence upon investigation of its safe and toxic levels. In 1964, the Food and Drug Administration issued a warning against the use of tannic acid in enemas. 1,10

For most drugs used in medicine, the margin between beneficial and undesirable results has been established. Radiologists must assume the responsibility not only of

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TABLE I LIVER FUNCTION STUDIES

Case No.	Sex and Age	Diagnosis	Diagnosis Liver Enema E		Barium Enema (cc.) Per Cent Expelled (estimated from post-evacuation roentgeno-			Liver Function Studies Numbers under headings below: 1 Before enema 2 After enema, 24 hr. 3 After enema, 3 da. 4 After enema, 7 da.					
						gram)	SGPT	DB	ТВ	LDH	LDH-P		
			G	roup 1. Cont	rol Group-	–No Tannic z	1cid						
1	F 2	Eczema and rectal bleeding		800	600	90	18	. I	.7	520 (a) 520	Normal >1, 2, 3,		
							1.2	. 1	. 5	(a)	(a)		
2	M 13	Peptic ulcer		1,000	1,000	95	10 20	· 3 · 1	.8	330	Normal Normal		
3	F 15	Appendicitis		1,000	1,200	60	18 14	.0 .05	.2 1.2 (b)	310 320	Normal Normal		
4	M 50	Bleeding hemorrhoids	Liver cirrhosis	000,1	1,600	75	17	. 2	1.2 (c) -3	430 (c) 390 (c)	Normal Normal		
5	F 52	Cancer of cervix; undergoing cobalt 60 therapy		1,000	1,800	95	14 16	.2	. 1	420 (d) 400 (d)	>LDH; (d) >LDH; (d)		
6	F 54	Duodenal ulcer	Cholelithiasis	1,000	1,200	60	14	. I	- 5	500 (e)	>1, 2 (e)		
							12	.0	.2	450 (e)	>1, 2 (e)		
7	F 58	Abdominal mass	TOTAL PROPERTY OF THE PARTY AND THE PARTY AN	1,000	I,700	95	4 2	.25	.80 .1	290 270	Normal Normal		
8	F 61	Diverticula		1,000	1,600	95	13	, o , I	.6	310 410 (f)	Normal Normal		
9	F 33	Peptic ulcer		1,000,1	1,800	85	1 6	.° ·3	.55	260 240	Normal Normal		
10	F 65	Diverticulosis		1,000	1,200	50	13 13	. I	. 55 - 55	260 280	Normal Normal		

Key to abbreviations:

- F
- Μ
- SGPT -Serum glutamic pyruvic transaminase (normal values 5-35 units)
- Direct bilirubin (normal less than 0.3 mg. %)

 Total bilirubin (normal less than 1.0 mg. %)
- LDH —Lactic acid dehydrogenase (100-350 units normal range)
- LDH-P-Lacticdehydrogenase isoenzyme patterns (increase in fractions 4 and 5 indicates liver abnormality)
- -Elevated

Footnotes:

- (a) Entire study repeated 5 weeks later after cleansing barium enemas showed almost identical abnormal LDH values and isoenzyme patterns.
 (b) No known explanation.
- (c) Liver cirrhosis may account for abnormal values.
- (d) Malignancy may account for abnormal values.
- (e) Cholelithiasis may account for abnormal values.
- (f) No increase in liver fractions.

Table 1 (Continued)

Case No.	Sex and Age	Diagnosis	Liver Abnormality	Cleansing Enema (cc.)	Barium Enema (cc.)	Per Cent Expelled (estimated from post- evacuation roentgeno-		Numb	iver Functiers under I Before e. After en After en After en	headings nema ema, 24 l ema, 3 d	below: hr. a.
						gram)	SGPT	DB	ТВ	LDH	LDH-P
				Group.	II. With T	annic Acid					
				0.25% Tannic Acid (cc.)	0.25% Tannic Acid (cc.)						
11	F 29	Urinary tract infection		1,000	1,600	95	1 I	.2	.4	260 280	Normal Normal
12	F 59	Abdominal pain		1,000	2,000	80	9 10	, I , I	.3	250 270	Normal Normal
13	M 33	Duodenal ulcer		1,000	1,100	95	6	. I	.6	245 250	Normal Normal
14	F 34	Pelvic cyst		1,000	1,800	90	22 25	.1	.5	230 280	Normal Normal
15	F 45	Pelvic tumor		000, 1	1,400	60	29 22	.o .1	.2	350 320	Normal Normal
16 (g)	M 82	Common bile duct obstruc- tion	Obstructive biliary cirrhosis	1,000	800	98	68 (g) 59 (g)	7.1 (g) 6.2 (g)	9.6 (g)	270	Normal Normal
17	F 52	Hematemesis; liver cirrhosis, delirium tremens	Liver cirrhosis	1,000	1,800	50	7	.0	.2	290 310	Normal Normal
18	F 49	Nausea, vomiting		1,000	1,100	75	6	·3	.8	340	Normal Normal
19	F 57	Colon carcinoma	Possible cirrhosis of liver	1,000	1,200	70	3 3	. I	· 3 . 2	260 290	Normal Normal
20	F 42	Cancer of pancreas		1,000	900	75	7 6	o. 1,	.9 .5	365 340	Normal Normal
			The Control of the Co	Group I	II. With T	Cannic Acid	~~~				
				0.25% Tannic Acid (cc.)	0.5% Tannic Acid (cc.)		4.00				The second secon
21	F 58	Pancreatitis		800	1,200	95	25 22	.3	.8	310 280	Normal Normal

⁽g) Admitted March 31, 1964 to Children's Hospital with history of jaundice and vomiting for 3 weeks. Gallbladder not visualized. Preoperative diagnosis: cholelithiasis with common duct obstruction. Barium enema on April 3, 1964, after which jaundice decreased and bilirubin levels dropped from 11.4 to 9.6.

creased and bilirubin levels dropped from 11.4 to 9.6.

Surgical removal of renal cyst, April 8, 1964. Surgical diagnosis: common bile duct obstruction by stone. Pancreatitis.

Postoperatively, marked drop in packed cell volume; shock. Died 24 hours after surgical procedure, April 9, 1964, 1:58 P.M. Clinical diagnosis: internal hemorrhage.

Postmortem examination done on April 9, 1964, 3:30 P.M. Postmortem diagnosis: (1) pancreatitis; (2) cholelithiasis; (3) hemorrhage into right peritoneal cavity and into perirenal tissues, severe, estimated 3,500 ml.; (4) arteriosclerosis, generalized, moderate; (5) fibrosis of myocardium, anterior wall left ventricle; (6) edema, lung, severe; (7) obstructive biliary cirrhosis of liver.

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Table 1 (Continued)

Case No.	Sex and Age	nd Diagnosis	Liver Abnormality	Cleansing Enema (cc.)	Barium Enema (cc.)	Per Cent Expelled (estimated from post- evacuation roentgeno-	To make a facility of the majors were and for the analysis and the substitute of the	Number 1 2 3	s under l Before en	neadings ema ma, 24 h ma, 3 da	na, 24 hr. na, 3 da.		
						gram)	SGPT	DB	ТВ	LDH	LDH-P		
22	M 18	Intestinal obstruction		I,000	1,700	75	25	.65 (h) .35 (h)	1.80 (h) 1.30 (h)	290 340	Normal Pattern normal with borderline fraction 5		
23	F 60	Abdominal mass		000,1	1,750	95	3 2	.0 .05	. 5 . 5	230 220	Normal Normal		
24	F 49	Vertebral compression fracture		1,500	1,000	95	14	. 2 . 1	.8 .3	260 270	Normal Normal		
25	F 60	Diverticulosis of colon		000, 1	1,000	90	13	. I	.3 ,2	280 270	Normal Normal		
26 (î)	F 42	Colitis	Ascariasis in past	1,000	750	90	12	. 2 . 3	.7 1.3 (i)	230	Normal Normal		
27	M 55	Diverticulosis of colon	and the second s	1,000	1,500	95	8	. 2 . I	.6 .2	225 210	Normal Normal		
28	F 73	Incomplete bowel rotation		1.000	900	90	IO IO	. 15	.6 .3	270 310	Normal Normal		
29	F 45	Ovarian carcinoma; abdominal metastasis and possible metastasis to liver	Possible metatasis to to liver	I ,000	1,000	75	19 23	.2	. 5	410 370	Normal Normal		
3°	M 52	Abdominal pain; unknown cause	Cirrhosis of liver	1,000	1.750	80	10 6	· 3 . I	.5	235 235	Normal Normal		
31	F 43	Abdominal pain		1,000	1,500	95	14	. I . I	.6 .8	320 320	Normal Normal		
32 (j)	F 58	Diverticulitis		1,000	600	95	0 0	. 2 . I	.6 .4	310 270	Normal Normal		
33	M 80	Arteriosclero- tic heart dis- ease; divertic- ulitis		1,000	1,500	90	50 47	.3 .15	1.2	460 330	Normal Normal		
34	F 51	Rectal bleeding		1,000	1,500	80	17 15	.0	.2	270 270	Normal Normal		
35	M 64	Hiatus hernia		1,000	1,250	95	10	. 2	.2	390 380	Normal Normal		
36	M 28	Hematemesis		1,000	1,200	85	14 13	. I . I	1.0	280 330	Normal Normal		

(h) Intestinal obstruction may account for abnormal values.

(i) Intestinal obstruction may account for abnormal values.
 (i) Entire test with enemas and liver functions repeated 5 weeks later showed normal values as follows: Before enema: SGPT 12; DB .15; TB .5; LDH 235; LDH-P normal. After enema: SGPT 13; DB .1; TB .2; LDH 250: LDH-P normal.
 (j) Liver biopsy 24 hours after tannic acid-containing enemas. On histologic examination, no tannic acid present and liver tissue account.

was normal.

TABLE I (Continued)

Case No.	Sex and Age	Diagnosis	Liver Abnormality	Cleansing Enema (cc.)	Barium Enema (cc.)	Per Cent Expelled (estimated from post- evacuation roentgeno-		Number 1 2 3	ver Funct rs under Before er After ene After ene	headings nema ema, 24 h ema, 3 da	below: r.
						gram)	SGPT	DB	ТВ	LDH	LDH-P
37	F 67	Lung metasta- sis, probably from colonic carcinoma		1,000	1,400	99	8 2	.1	.6 ·4	37° 37°	Normal Normal
38	F 23	Peptic ulcer		1,∞∞	1,8∞	85	5	. I •4	.2 1.6 (k)	330 330	Normal Normal
39	M 5 mo.	Failure to thrive		1,000	100	15	17	.1	•4	520 (1)	Elevated LDH 1, 2, 3; especially LDH2
							26	.1	.2	760 (1)	Elevated LDH 1, 2, 3; especially LDH2
40	F	Abdominal		500	800	40	7	.2	1.4	310	Normal
	4	mass					22	.ı	(1)	47° (l)	Normal
4 I	F 57	Colonic polyps		1,000	1,500	80	5 4 11 11	.2 .1 .1	1.0 .6 .2	325 360 340 320	Normal Normal Normal Normal
42	F 64	Colectomy for carcinoma		1,000	1,200	90	13 15 15 12	.2 .1 .1	1.3 .3 .4 .2	290 270 300 310	Normal Normal Normal Normal
43	F	Lymphatic	Hepatospleno-	1,000	1,700	99	25	.4	1.1	740	>1,2,3
	70	leukemia (m)	megaly (m)				47	.5	1.0	650	(m) >1, 2, 3
							21	.2	1.0	605	(m) >1, 2, 3
							12	•3	.6	620	(m) >1, 2, 3, 4 (m)
44	F	Cholecystitis	Cholecystitis, cholelithiasis	1,000	2,000	75	10	. I	.5	290	Normal
	71	(n)	CHOIGHUMSIS				(n) 11 (n)	. 1	.6	335	Normal
							7 (n)	.2	.9	290	Normal
							38 (n)	-4	1.0	350	Normal
45	F 7º	Rectal bleeding		1,000	950	80	8 8 12 11	-3 .1 .2	.8 •4 •4 1.0	250 290 315 270	Normal Normal Normal Normal

⁽k) Entire enema study and liver profile examination repeated 7 weeks later with following results: Before enema: SGPT 22; DB .3; TB .8; LDH 390; LDH-P normal. After enema: SGPT 19; DB .1; TB .2; LDH 390; LDH-P normal.
(l) Liver isoenzyme levels normal.
(m) Liver fractions normal.
(n) Cholecystectomy between third and seventh day because of cholelithiasis. Anesthesia with fluothane. Liver profile study repeated 18 days after final enema showed the following: SGPT 30; DB .1; TB .4; LDH 440; LDH-P normal.

TABLE I (Continued)

Case No.	Sex and Age	Diagnosis	Liver Abnormality	Cleansing Enema (cc.)	Barium Enema (cc.)	Per Cent Expelled (estimated from post- evacuation roentgeno-		Numbe 1 2 3	ver Functions under l Before en After ene After ene After ene	headings nema ema, 24 h ema, 3 da	below: ur.
	l					gram)	SGPT	DB	ТВ	LDH	LDH-P
46	F 25	Bleeding of aorta		1,000	1,200	70	11 10 5 14	.I .I .I5	.2 .1 .20 .6	290 250 230 270	Normal Normal Normal Normal
47	F 63	Peptic ulcer		1,000	1,200	8 0	10 11 10	.3 .3 .2	.8 .8 1.1 1.0	270 290 380 300	Normal Normal Normal Normal
48	F 50	Diverticulitis		1,000	1,000	99	10 8 12 10	.0 .0 .2	.2 .2 .8	320 370 315 345	Normal Normal Normal Normal
49	F 36	Rectal bleeding;		1,000	1,400	85	97	.5	.20	400	>1, 2 (m)
		sickle-cell anemia (m)					71	.1	.4	445 4∞	>1 (m)
							F	nema I	days lat	er:	(m)
								.2	.6	(m)	
50	F 37	Rectal bleeding		1,000	1,800	90	66	.0	.2	290	Normal
	g,	J					C		r function at 24 hou		
							24 19	. 2 .0	.8 .1	310 325	Normal Normal
51	F 33	Melanosar- coma	Liver metastasis	1,000	1,200	90	27	.2	.6	335	>1, 2, 3, 4, 5
							30	-4	.6	400	>1, 2, 3, 4, 5
							20 14	.2 .1	• 4 •4	355 325	>1, 2, 3, 4, 5 >1, 2, 3, 4, 5
52	F	Hypoglycemia		1,000	1,500	90	26	.2 .1	.5	280 260	Normal Normal
	50						29 30	.1	·4 .2	280	Normal
					,		34	.1	.2	250	Normal
53	F 70	Melena and possible myo-		1,000	1,000	75	3 4	.1 .1	, 8 .6	290 270	>1, 2 >1, 2
		cardial infarct					4	.2	-4	290	>1, 2
							6	.1	4	280	>1, 2
54	F 69	Uterine fibroid		1,000	1,500	70	7	. I	.6	420 (0)	Normal
							7	.0	.4	450 (o)	Normal
							6	.1	.6	4∞ (o)	>1
						Ì]	Enema 5	days late	er	
							8	.15	.3	42 0 (0)	>1
55	F	Duodenal		1,000	1,500	50	7	. 1	-4	240	Normal
1											
	37	ulcer					10 5	.0	.2	270 355	Normal Normal

⁽⁰⁾ LDH elevated before and after enemas, Elevation in fraction 1 suggestive of myocardial infarct. Liver profile study repeated

investigating the efficacy of tannic acid, but of establishing a dosage of reliable safety. The information presented in the medical literature points to tannic acid as the best available agent for colonic cleansing and mucosal delineation. ^{5,16,19,20,24} A large-scale objective study of the efficacy of tannic acid is now underway. ¹² To limit the radiologist's resources in such an important examination as that of the colon without scientific investigation would indeed be a grave error.

SUMMARY

Recent reports have emphasized that tannic acid, a time-honored agent in barium enema examinations, may cause severe side reactions.

Studies of liver function in 45 patients indicate the safety of enemas with tannic acid when used in the following dosage: 0.25 per cent tannic acid* in the cleansing enema and 0.5 per cent regular tannic acid in the barium enema mixture.

Since tannic acid appears to have both a safe and a toxic dose range, accurate measurement is of utmost importance. Standardized individual packaging of tannic acid is thus recommended.

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We are grateful to the medical staff of Children's Hospital who permitted inclusion of their private patients in this study.

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≈ EDITORIAL ×

THE PROBLEM OF TANNIC ACID IN COLON EXAMINATIONS

ANNIC acid was shown to be a potent hepatotoxin by Wells et al.1 in 1942, when it was routinely used in the topical treatment of burns. It was reputed to promote healing, prevent infection, and induce the formation of a thick eschar which was sometimes difficult to remove. The livers of those who died following this treatment exhibited a centrilobular type of hepatic necrosis. Wells and his co-workers proved that the deaths were not due to toxemia but to absorption of tannic acid through burned skin surfaces. In 1943, Baker and Handler2 reported the production of hepatic necrosis in mice following the subcutaneous injection of tannic acid in concentrations of I per cent or more.

Hamilton³ in 1946, published a brief article recommending the use of tannic acid in barium enema examinations in a dose of one tablespoon to every two quarts of barium enema mixture. He produced excellent roentgenograms showing minute mucosal detail permitting, for the first time, the detection of small mucosal lesions. The technique was so satisfactory that it was made a routine at the Army General Hospital to which he was assigned. No adverse effects or symptoms were encountered in his series; however, no experimental work was done to establish safe and effective dose levels.

Tannic acid is a complex glucosidic poly-

¹ Wells, D. B., Humphrey, H. D., and Coll, J. J. Relation of tannic acid to liver necrosis occurring in burns. *New England J. Med.*, 1942, 226, 629-636.

² Baker, R. D., and Handler, P. Animal experiments with tannic acid suggested by tannic acid treatment of burns. Ann. Surg. 1022, 118, 117-127.

Surg., 1943, 178, 417-427.

³ Hamilton, J. B. Use of tennic acid in barium enemas. Am. J. ROENTGENOL. & RAD. THERAPY, 1946, 56, 101-103.

ester of gallic acid and related phenolic acids with a molecular weight in the range of 1,500 to 2,000. By virtue of its astringent properties, it stimulates contraction of the colon and causes barium to adhere to the bowel wall. It also inhibits the secretion of mucin and produces precipitation of protein in the superficial layers of the mucosa. This latter property has been taken advantage of formerly in the treatment of irritative lesions of the bowel, such as ulcerative colitis and dysentery, in which a protective coating of the mucosa was desired.

There is no doubt that the quality of the barium enema examination was significantly enhanced by the addition of tannic acid and, therefore, its popularity grew. Thomas, in 1963, estimated that over 600,000 patients received annually barium enemas containing tannic acid. The quantity of tannic acid used was determined by the individual radiologist performing the examination and varied from 0.5 per cent to 3.0 per cent.

In 1950, Christie et al.⁶ advocated using 1 gm. of tannic acid to 100 cc. of the barium and water mixture, stating that the low concentrations will give no effect and high concentrations would cause excessive

⁴ Thomas, S. F. All speed and no control. Editorial. Am. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1963, 89, 889-890.

^{*} STEINBACE, H. L., and BURHENNE, H. J. Performing barium enema: equipment, preparation, and contrast medium. AM. J. ROEMTOENOL., RAD. THERAPY & NUCLEAR MED., 1962, 87, 644-644.

<sup>654.

6</sup> Christie, A. C., Coe, F. O., Hampton, A. O., and Wyatt, G. M. Value of tannic acid enema and post-evacuation roent-genograms in examination of colon. Am. J. Roentgenol. & Rad. Therapy, 1950, 63, 657–664.

abdominal cramps. Welin, in 1958, describing his double contrast technique, used tannic acid in the cleansing enema, the barium enema and the double contrast enema. In 1962, Steinbach and Burhenne recommended the use of a clysodrast cleansing enema containing 2.5 gm. of tannic acid followed by a barium enema containing 0.8 to 1.0 per cent tannic acid. In none of these large series had any known unfavorable sequelae occurred.

Then, in 1963, McAlister et al.8 reported deaths in 3 children from hepatic necrosis, each of whom had received enemas containing 0.75 per cent tannic acid. The first patient, a 10 year old boy, was given 3 normal saline enemas on the initial hospital day. The next morning he received 2 preparatory saline enemas and I barium enema, all containing 0.75 per cent tannic acid. Poor evacuation of the barium was demonstrated. He later showed evidence of metabolic acidosis, became deeply jaundiced and died on the seventh postenema day. At autopsy, tannic acid was demonstrated in the liver. The second patient, a 4 month old female, was treated with stool softeners and daily saline enemas because of constipation. Nine days after admission, a barium enema with 0.75 per cent tannic acid was administered following a preparatory enema containing 0.75 per cent tannic acid. The patient went into shock and died 48 hours later. The third patient, a 5 year old female, was admitted because of recurrent abdominal pain. On the day of admission, 2 saline enemas and a Dulcolax suppository were given. On the third day, I preparatory and I barium enema were administered, both containing 0.75 per cent tannic acid. There was poor evacuation of the enema. Death occurred 72 hours later. Autopsy findings in the last two patients revealed hepatic necrosis.

⁷ Wellin, S. Modern trends in diagnostic roentgenology of colon. Mackenzie Davidson Memorial Lecture. *Brit. J. Radiol.*, 1958, 31, 453-464.

Subsequent experimental studies on animals by McAlister et al.⁸ indicated absorption of tannic acid through the intact colonic mucosa. However, the method they used to detect serum tannic acid levels is not specific for tannic acid, since most free phenolic-like compounds will yield the same result spectrophotometrically. Thus, gallic acid, the predominant hydrolytic product of tannic acid probably could not have been distinguished from tannic acid.¹⁸

Stimulated by the report of McAlister and co-workers, Lucke et al. re-investigated 5 cases of early death from liver failure occurring in their hospital over a 3 year period. All 5 patients had had barium enemas containing 2 per cent tannic acid within 1 to 6 days prior to death. At autopsy, their livers showed extensive centrilobular necrosis. Although there was no definite proof that tannic acid was responsible for these deaths, since the livers had been fixed and assay for tannic acid is not possible under these circumstances, this possibility was certainly entertained.

Radiologists, in general, were disturbed by these reports and several clinical and experimental investigations were undertaken designed to determine the safety of tannic acid when used within certain well defined limits. Employing an extremely sensitive index of liver integrity, the serum glutamic oxalacetic transaminase (SGOT) determination, Staab and Vix10 were unable to demonstrate a significant rise in 92 of 94 patients subjected to barium enemas with 0.25 per cent added tannic acid. The change in the SGOT level was borderline in I patient, a 71 year old male, who had regional ileitis. The other patient, a 68 year old diabetic male, had a definite rise in the SGOT level, which in view of an abnormal electrocardiographic pattern was probably the result of coronary artery disease and myocardial damage.

^{1958, 31, 453-464.}MCALISTER, W. H., ANDERSON, M. S., BLOOMBERO, G. R., and MAROULIS, A. R. Lethal effects of tannic acid in barium enema: report of three fatalities and experimental studies. Radiology, 1963, 80, 765-773.

⁹ LUCKE, H. H., HODGE, K. E., and PATT, N. L. Fatal liver damage after barium enemas containing tannic acid. Canad. M. A. 7., 1967, 80, 1111-1114.

M. A. J., 1963, 89, 1111-1114.

10 Staab, E. V., and Vix, V. A. Serum glutamic oxalacetic transaminase levels following tannic acid enemas. Radiology, 1965, 84, 1087-1089.

In a retrospective study, Janower et al.¹¹ reviewed the case histories of all cases of acute hepatic death at the Massachusetts General Hospital over a 17 year period, from 1947 to 1963. Of 76 patients who met the requirements of the study, 10 had received a barium enema from 1 day to 48 months prior to death. In only 1 of these cases was there the least suspicion that the barium enema might have been implicated.

In this issue of the JOURNAL, 5 outstanding articles are published defining certain facets of the effect of tannic acid when administered for colon examination. Margulis and his associates12-14 demonstrated by animal experimentation (on rats) that 3 consecutive I minute retention enemas given at hour intervals did not produce liver damage in animals sacrificed at 72 hours, when concentrations of tannic acid of 0.25 to 2.0 per cent were used. However, following forced I hour retention enemas, liver damage was detected at the 2.5 per cent level. Absorption of tannic acid through the intact mucosa was studied by utilizing a new method of thin layer chromatography. No detectable amounts could be demonstrated in the portal vein blood samples after instillation of I per cent tannic acid enemas even though retained for I hour. Minute amounts were detected after instillation of a 2 per cent tannic acid enema forcibly retained for I minute. Thus, increased concentration of tannic acid in the

¹¹ Janower, M. L., Robbins, L. L., Tomchik, F. S., and Weylman, W. T. Tannic acid and barium enema. *Radiology*, 1065, 85, 887-804.

enema and increased retention of the enema result in greater absorption of tannic acid. Experimentally, it was shown that the colon must be previously damaged before tannic acid can be absorbed. Even preparatory enemas of isotonic saline can produce edema and inflammation of the mucosa, creating a possible avenue for the absorption of tannic acid. This may be the explanation for the deaths in the series of McAlister et al., since all of their patients received multiple enemas. In the series of Lucke et al., 2 per cent tannic acid was used in the barium sulfate enemas. In the light of our present knowledge, this concentration may be toxic if the enema was retained long enough or other interacting variables existed.

As a result of their exhaustive investigations, Margulis and his co-workers state: "There is no proof that a tannic acid enema in a concentration of 0.25 and 0.5 per cent has ever produced hepatotoxicity."

A similar conclusion is reached by Burhenne and his associates¹⁵ who performed a detailed clinical study of the liver function in 45 patients. No significant alteration of the liver function was noted after a cleansing enema containing 0.25 per cent tannic acid and a barium enema mixture with 0.5 per cent added tannic acid.

Conceivably, other important investigations will be carried out in the near future, in particular on the role of the interacting factors. The data obtained so far indicate a good margin of safety which, however, may be narrowed by these factors. Accurate measurement of the dose and precise evaluation of the possible interacting factors are, therefore, prerequisites of any colon examination in which tannic acid is used.

FRANCIS P. SHEA, M.D.

Harper Hospital Detroit, Michigan 48201

<sup>1965, 85, 887-894.

12</sup> RAMBO, O. N., ZBORALSKE, F. F., HARRIS, P. A., RIEGELMAN, S., and MARQULIS, A. R. Toxicity studies on transic acid administered by enema. I. Effects of enema-administered tannic acid on colon and liver of rats. Am. J. Roemandom, Rad. Therapy & Nuclear Med., 1965, 96, 488-497.

13 HARRIS, P. A., ZBORALSKE, F. F., RAMBO, O. N., MARGULIS,

¹³ Harris, P. A., Zboralske, F. F., Rambo, O. N., Margulis, A. R., and Riegelman, S. Toxicity studies on tannic acid administered by enema, II. Colonic absorption and intraperitoneal toxicity of tannic acid and its hydrolytic products in rats. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1966, 96, 468-

^{504.}M ZBORALSKE, F. F., HARRIS, P. A., RIEGELMAN, S., RAMBO, O. N., and MAROULIS, A. R. Toxicity studies on tennic acid administered by enema. III. Studies on retention of enemas in human. IV. Review and conclusions. Am. J. ROENTORNOL., RAD. THERAPY & NUCLEAR MED., 1966, 96, 505-509.

¹³ BURHENNE, H. J., VOGELAAR, P., and ARKOFF, R. S. Liver function studies in patients receiving enemas containing tannic acid. Am. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1966, 96, 510-518.

NEWS ITEMS

NEW OFFICERS OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

At the Fifty-first Annual Meeting of the Radiological Society of North America held November 28-December 3, 1965 at the Palmer House in Chicago, Illinois, the following officers were elected: President— John W. Walker, M.D., Kansas City, Missouri; President-Elect—Harold G. Jacobson, M.D., New York, New York; First Vice-President—Seymour F. Ochsner, M.D., New Orleans, Louisiana; Second Vice-President—David M.D., Kirsh, Miami, Florida; Third Vice-President— Vernon L. Bolton, M.D., Colorado Springs, Colorado; Secretary-Treasurer—Maurice D. Frazer, M.D., Lincoln, Nebraska; and Historian—Howard P. Doub, M.D., Detroit, Michigan.

The Chairman of the Board of Directors is Stanley M. Wyman, Belmont, Massachusetts.

The Gold Medal of the Society was awarded to Marvin M. D. Williams, Ph.D., Rochester, Minnesota.

The Fifty-second Annual Meeting of the Society will be held November 27-December 2, 1966 at the Palmer House in Chicago, Illinois.

SECTION ON RADIOLOGY OF THE SOUTHERN MEDICAL ASSOCIATION

The Section on Radiology of the Southern Medical Association announces the election of the following officers to serve for the coming year: Robert N. Cooley, M.D., Galveston, Texas, *Chairman*; Raymond E. Parks, M.D., Miami, Florida, *Vice-Chairman*; Andrew F. Giesen, Jr., M.D., Fort Walton Beach, Florida, *Secretary*.

These officers will be responsible for arranging the program for the Section on Radiology for the 60th Annual Meeting of the Association which will be held in Washington, D.C., November 14–17, 1966.

Anyone wishing to participate in the program should contact the Secretary of the

Section, Andrew F. Giesen, Jr., M.D., White-Wilson Clinic, Drawer M-M, Fort Walton Beach, Florida 32548.

Application forms for scientific exhibit space can be obtained from the Southern Medical Association, 2601 Highland Avenue, Birmingham, Alabama 35205.

POSTGRADUATE COURSE IN ROENT-GENOLOGY OF THE ABDOMEN

The Department of Radiology of the Medical College of Virginia is planning a postgraduate course in "Roentgenology of the Abdomen," with emphasis on topics of practical importance, March 1–5, 1966, at the New Conference Center, Williamsburg, Virginia.

The Guest Faculty includes: Dr. John L. Emmett, Dr. Ragnar Bjorn-Hansen, Dr. Richard H. Marshak, Dr. Charles D. Noonan, Dr. Antolin Raventos, Dr. E. Clinton Texter and Mr. Floyd L. Thompson.

The program is designed to cover topics of practical importance of interest to practicing radiologists, gastroenterologists, obstetricians, gynecologists and urologists.

For additional information contact: M. Pinson Neal, Jr., M.D., Director, Post-graduate Courses, Department of Radiology, Medical College of Virginia, 1200 East Broad Street, Richmond, Virginia.

SPRING CONFERENCE OF THE NEW YORK ROENTGEN SOCIETY

The New York Roentgen Society will hold its Annual Spring Conference at the Waldorf-Astoria Hotel, on April 21, 22, and 23, 1966.

The Scientific Program will feature refresher courses as well as papers on subjects of current interest.

Dr. Russell H. Morgan, Professor of Radiology, The Johns Hopkins School of Medicine, will give the Annual Ross Golden Lecture.

For additional information write to

Albert A. Dunn, M.D., Roosevelt Hospital, 428 W. 59th Street, New York, New York 10019.

SYMPOSIUM ON OSTEOSARCOMA

A two day Symposium on Osteosarcoma will be held at the Ohio State University College of Medicine, under the direction of the Division of Orthopaedics, on April 15–16, 1966.

The faculty will consist of authorities in this field, among whom are Sir Stanford Cade, Dr. H. A. Sissons, Dr. David Dahlin, Dr. Harold Jacox, Dr. Kenneth Francis and Dr. Jonathan Cohen.

The symposium will comprise talks and panel discussions on the epidemiology, diagnosis, and, most particularly, treatment of osteosarcoma. Emphasis will also be placed on recent developments such as immunologic factors, chemotherapy, and the potential use of the laser.

Application for attendance should be made to Paul H. Curtiss, Jr., M.D., Center for Continuing Medical Education, A-352 Starling Loving Hall, 320 West Tenth Avenue, Columbus, Ohio 43210.

SYMPOSIUM OF CARDIOVASCULAR DISEASE

A Symposium on Cardiovascular Disease will be presented by the Department of Radiology of the University of Kentucky Medical Center from May 2 to May 6, 1966, immediately preceding the Kentucky Derby.

Besides staff members of the University of Kentucky, the outstanding guest faculty will include: Dr. Herbert L. Abrams, Stanford University; Dr. John A. Campbell, University of Indiana; Dr. Benjamin Felson, University of Cincinnati; Dr. Mordecai R. Halpern, University of Southern California; Dr. Daniel J. Hanson, Roger Williams Hospital, Providence; Dr. G. B. C. Harris, Children's Hospital Medical Center, Boston; Dr. R. Brian Holmes, University of Toronto; Dr. Joseph Jorgens, VA Hospital, Minneapolis; Dr. John Keith, Hospital for Sick Children, Toronto; Dr. Eugene C. Klatte, Vanderbilt University;

Dr. J. Stauffer Lehman, Hahnemann Medical College; Dr. Richard G. Lester, Duke University; Dr. Thomas R. Marshall, University of Louisville; and Dr. R. Van Praagh, Hektoen Institute for Medical Research, Chicago.

Inquiries concerning this Symposium should be addressed to Dr. Nicholas J. Pisacano, Director of Continuing Medical Education, University of Kentucky Medical Center, Lexington, Kentucky 40506.

ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, INC.

The scientific sessions of the Fifty-seventh Annual Meeting of the American Association for Cancer Research, Inc., will be held at the Hilton Hotel, Denver, Colorado, from 9:00 A.M., Thursday, May 26, to 5:00 P.M., Saturday, May 28, 1966.

Registration will be conducted on the evening of May 25 and during the course of the meeting. Nonmembers may obtain programs and purchase abstracts of the papers at the time of registration. By action of the Board of Directors, a registration fee of \$12.00 will be charged each member and nonmember attending the scientific sessions of this meeting; a special rate of \$5.00 will be charged medical and graduate students who present a statement, signed by the registrar or a dean of their university, confirming their status as students.

The regulations concerning abstracts and presentation of papers must be followed carefully.

For further information contact: Hugh H. Creech, Secretary-Treasurer, American Association for Cancer Research, Inc., The Institute for Cancer Research, Fox Chase, Philadelphia, Pennsylvania 19111.

THE BRITISH INSTITUTE OF RADIOLOGY

The Twenty-seventh Annual Congress and Scientific Exhibition of the British Institute of Radiology will be held Thursday and Friday, March 31 and April 1, 1966 at the School of Pharmacy, Brunswick Square 29–39, London, W.I.

The Congress will be opened by the President, Miss M. D. Snelling at 10:30 A.M. Thursday, and the Opening Address will be delivered by Professor Sir Charles Dodds. After a visit to the Scientific Exhibition, at 12:00 NOON Professor E. B. Chain will give the Mackenzie Davidson Memorial Lecture.

Thursday afternoon there will be a Joint Meeting of the Sections of Radiodiagnosis and Radiotherapy, the topic being "The Detection and Management of Subclinical Metastases."

On Friday the two Sections will meet

separately. The topics to be discussed at the Section of Radiodiagnosis are: "The Radiological Investigation of the Larynx and Hypopharynx" in the forenoon and the "Radiological Examination of the Spinal Cord and Nerve Roots" in the afternoon; and at the Section of Radiotherapy: "Preoperative Irradiation" in the forenoon and "Advances in Dosimetry and Technique" in the afternoon.

For further details write to: G. H. du Boulay, M.B., B.S., D.M.R.D., F.F.R., Honorary Medical Secretary, 32 Welbeck Street, London W.I., England.

DR. HOWARD P. DOUB HONORED

Dr. Howard P. Doub, the illustrious Editor of Radiology, was honored on the occasion of his retirement, in a special ceremony at the recent Annual Meeting of the Radiological Society of North America, held November 28-December 3, 1965 in Chicago, Illinois.

Dr. Doub, Past President and Gold Medalist of both the Radiological Society of North America and the American College of Radiology, was Editor of Radiology since 1941. During this period, by his unflinching devotion to science, his inborn reverence for scholarly attainments, his consecration to ideals and above all his great vision of the future, he skillfully steered the helm of Radiology, in making it one of the world's leading radiologic periodicals.

Appropriately, Dr. Robert D. Moreton, President of the Radiological Society of North America, presented him with a scroll on which is written:

To HOWARD PHILIP DOUB, M.D.

For a quarter of a century you have chartered the course of our journal with an unerring sense of direction. You have provided leadership with quiet, firm decisions based on impartiality and fairness to all. Your search for merit in men and manuscripts, personnel and papers, has brought to the pages of Radiology the best efforts of radiologic scientists and to the consulting staff distinguished authorities from several disciplines.

Your example of scholarship and your equanimity have been an inspiration to those around you. The Radiological Society of North America has elected you EDITOR EIAERII US FOR LIFE and presents this scroll to you as a token of esteem and affection and in recognition of the services which have earned for you a unique and secure place in the history of this science and of this society.



BOOK REVIEW

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

SURGERY OF THE CHEST. Edited by John H. Gibbon, Jr., M.D., Chairman of the Department of Surgery, Jefferson Medical College, Philadelphia, Pa. Cloth. Price, \$27.00. Pp. 902, with many illustrations. W. B. Saunders Company, West Washington Square, Philadelphia, Pa., 1962.

This book has been edited by one of the pioneers of thoracic and cardiovascular surgery. With the collaboration of 35 outstanding authorities in this specialty, he has put forth a very well organized, practical text on thoracic surgery. The text is divided into 33 chapters, beginning, as it should, with the cardiorespiratory dynamics of the thorax.

All the chapters are well written and excel-

lently illustrated.

The book makes for easy and interesting reading because each author has been allowed to write in his own inimitable style. The general principles of thoracic surgery have been emphasized more than the minute details, thus providing an excellent source of reference for the medical student, as well as for the specialist.

This is not an "Atlas" of thoracic surgery, although sufficient detail of the more common procedures is presented and well illustrated.

Despite the fact that this book is already 4 years old, having been published in 1962, it still is an invaluable reference source and is highly recommended.

Francis S. Gerbasi, M.D.

BOOKS RECEIVED

THE GASTROINTESTINAL TRACT: A HANDBOOK OF ROENTGEN DIAGNOSIS. Second edition. By Fred Jenner Hodges, B.S., M.D., Professor; and Walter MacIntire Whitehouse, A.B., M.S., M.D., Professor, Department of Radiology, University of Michigan Medical School, Ann Arbor, Mich. Cloth. Pp. 384, with 160 plates. Price \$12.00. Year Book Medical Publishers, Inc., 35 E. Wacker Drive, Chicago, 1965.

The Essentials of Roentgen Interpretation. Second edition. By Lester W. Paul, M.D., Professor of Radiology, The University of Wisconsin Medical School; and John H. Juhl, M.D., Professor of Radiology, Chairman of Department of Radiology, The University of Wisconsin Medical School. Cloth. Pp. 902, with 1,263 illustrations. Price, \$25.00. Hoeber Medical Division, Harper & Row, Publishers, 49 E. 33rd Street, New York, N.Y., 1965.

FIFTH NATIONAL CANCER CONFERENCE PROCEEDINGS. Philadelphia, Pa., Sept. 17–19, 1964. Sponsored by American Cancer Society, Inc., and National Cancer Institute. Cloth. Pp. 764, with many illustrations. Price, \$10.00. J. B. Lippincott Company, East Washington Square, Philadelphia, Pa.,

1965.

AN OUTLINE OF RADIOGRAPHIC FINDINGS IN MULTIPLE-SYSTEM DISEASE. By John H. Simonton, M.D., Assistant Professor of Radiology (in residence), University of California at Los Angeles; Assistant Chief Radiology, Department of Radiology, Los Angeles County Hospital, Torrance, Calif.; and Robert C. Jamison, M.D., Assistant Professor of Radiology (in residence), University of California at Los Angeles; Radiologist in Charge of Diagnosis, Department of Radiology, Los Angeles County Harbor General Hospital, Torrance, Calif. Cloth. Pp. 261. Price, \$11.75. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1965.

Progress in Biochemical Pharmacology. Volume I. First International Symposium on Radiosensitizers and Radioprotective Drugs, Milan, 1964. Edited by R. Paoletti, and R. Vertua, Milan. Cloth. Pp. 760, with 287 figures and 158 tables. Price, \$28.50. Butterworth Inc., 7300 Pearl Street,

Washington 14, D. C., 1965.

Radiologic Diagnosis in Infants and Children. By Armand E. Brodeur, M.D., M.Rd., F.A.C.R., Chief Radiologist, Cardinal Glennon Memorial Hospital for Children, St. Louis, Mo.; Associate Professor Radiology and Associate Dean, St. Louis University School of Medicine; Medical Director, School of X-ray Technology, St. Louis University, St. Louis, Mo.; Chairman, Committee on Public Education, American College of Radiology; Consultant to Division of Radiological Health of United States Public Health Service and to The Catholic Hospital Association of the United States and Canada. Cloth. Pp. 503, with 757 illustrations. Price, \$26.50. C. V. Mosby Company, Publishers, 3207 Washington Blvd., St. Louis, Mo., 1065.

THE TRAIL OF THE INVISIBLE LIGHT. From X-Strahlen to Radio(bio)logy. By E. R. N. Grigg, M.D., Attending Radiologist, Cook County Hospital, Chicago; Consulting Radiologist to the Illinois Department of Public Welfare and to the hospitals in Charleston, Harvard, Paris, and Paxton, Ill. Cloth. Pp. 974, with many illustrations. Price, \$36.75. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1965.

GASTROENTEROLOGY. Volume III. Second edition. By Henry L. Bockus, M.D., Emeritus Professor of Medicine, University of Pennsylvania Graduate School of Medicine; and Present and Former Colleagues at the University of Pennsylvania Graduate School of Medicine, and School of Medicine. Cloth. Pp. 1,352, with many illustrations. Price, \$30.00. W. B. Saunders Company, Philadelphia, Pa., 1965.

Personnel Dosimetry for Radiation Accidents.

Proceedings of a Symposium on Personnel Dosimetry for Accidental High-level Exposure to External and Internal Radiation. Held jointly by the International Atomic Energy Agency and the World Health Organization, Vienna, March 8-12,

1965. Cloth. Pp. 714, with some figures. Price, \$14.00. International Publications, Inc., 317 East 34th Street, New York, N. Y., 1965.

RÖNTGENANATOMIE. By Prof. Dr. Dénes Nagy. Cloth. Pp. 520, with 545 illustrations. Price,\$14.00. Akadémiai Kiadó, Publishing House of the Hungarian Academy of Sciences, Alkotmány U. 21, Budapest, Hungary, 1965.

URINARY TRYPSIN INHIBITOR IN MAN ("MINGIN"). Physiological and Pathc-physiological Variations, Relation to Pituitary-Edrenocortical Hormones, and to Serum Trypsin Inhibitor. By Hans Jørgen Faarvang. Paper. Pp. 78. The Scandinavian Journal of Clinical & Laboratory Investigation. Volume 17, Supplementum 83. Munksgaard, Copenhagen, 1965.

STUDIES IN HAEMATOLOGY. A Tribute to Professor Paul A. Owren on the Occasion of his 60th birthday, August 27, 1965. Head editor, Helge Stormorken. Paper. Pp. 261, with many illustrations. The Scandinavian Journal of Clinical & Laboratory Investigation. Volume 17, Supplementum 84. Universitetsforlaget, Norway, 1965.

It is with deep regret that we announce the death on December 20, 1965, in Boston, Massachusetts, of Dr. Frederick W. O'Brien, Past President of the American Radium Society and Life Member of the American Roentgen Ray Society.



ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

HEAD

Asherson, R. A., Jackson, W. P. U., and Lewis, B. Abnormalities of development associated with hypothalamic calcification after tuberculous meningitis. *Brit. M. J.*, Oct. 9, 1965, 2, 839–843. (From: Department of Medicine, Groote Schuur Hospital and University of Capetown, South Africa.)

The authors review 3 cases of endocrine syndromes subsequent to tuberculous meningitis. Two of the male youths, ages 17 and 19, had obesity, delayed bone development, and hypogonadism ("Fröhlich syndrome"); precocious sexual development was observed in the other patient, a 9 year old. Calcification in the suprasellar region was demonstrated on roentgenograms in all patients, confirming the probability that damage to the hypothalamus was the cause of the disorder.

Results from animal experimentation suggest that the anterior hypothalamus and its interconnections exert a tonic inhibitory control over gonadotrophin secretion in the prepubertal animal and that hypothalamic lesions, by reducing the area from which pituitary-inhibiting stimuli arise, may initiate precocious puberty. In cases of gonadal depression, the inferior and more anterior regions of the hypothalamus were the sites of the lesions.

Data from other research show conclusively the profound influence of third-ventricle tumors and internal hydrocephalus on sexual maturation.—

Lois Cowan Collins, M.D.

Hunter, Douglas D. Pulmonary arteriovenous malformation: an unusual cause of cerebral embolism. *Canad. M. A. J.*, Sept. 18, 1965, 93, 662-665. (From: Department of Medicine, Toronto Western Hospital, Toronto, Ontario, Canada.)

A case is reported of a cerebral vascular accident due to a cerebral embolus arising from a pulmonary arteriovenous malformation. The author did not encounter a similar case in a search of the literature.

Pulmonary arteriovenous malformations were first described in autopsy reports in 1897, in 1917, and again in 1932. The first clinical diagnosis was made in 1939 and the first surgical correction in 1942. In most of the cases described in the literature the lesion was a manifestation of hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber-disease), in which the lesions may be evident in the gastrointestinal, genitourinary, or respiratory systems as well as involving the mucous membranes of the nose and mouth.

When poorly oxygenated blood is shunted through a pulmonary arteriovenous fistula, the resulting

anoxemia is responsible for anoxic stimulation of the bone marrow, cyanosis, clubbing of the distal phalanges, dyspnea on exertion, epistaxis, or hemoptysis. Most of the central nervous system symptoms and signs associated with pulmonary arteriovenous fistulas are attributed to the compensatory polycythemia although hemiparesis due to brain abscess has been reported.

The author reports a case of an 18 year old girl, previously asymptomatic, who had hemiplegia of sudden onset resulting from a cerebral embolus. Multiple pulmonary arteriovenous malformations were identified by means of pulmonary catheterization studies and one of these, in which the contrast material pooled and emptied slowly, was considered the possible origin of the embolus. Polycythemia was not present. Surgical excision of 2 of the pulmonary arteriovenous malformations was carried out successfully.—James R. Knapp, M.D.

NECK AND CHEST

REISNER, K., and Huzly, A. Die sogenannten Perikardzysten, ihre Differentialdiagnose und Ätiologie. (Differential diagnosis and etiology of pericardial cysts.) Fortschr a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin, July, 1965, 103, 1-20. (Address: Dr. K. Reisner, Institut für klinische Strahlenkunde, Universitätskliniken Mainz, Langenbeckstr. 1. 6500 Mainz, Germany.)

Indicative of some confusion concerning pericardial cysts is the list of synonyms found in the literature: celomic cyst, mesothelial cyst, pleurodiaphragmatic cyst, celeothelioma, "Spring water cyst" and pericardial diverticulum. True pericardial cysts are found only in the anterior mediastinum. In 12 of 18 cases confirmed by surgery, 9 were located on the right and 3 on the left side (all were covered by mediastinal pleura and only one cyst had a typical stalk attached to the pericardium).

The roentgenographic characteristics of pericardial cysts include: (1) round or oval, sharply demarcated density in the anterior cardio-diaphragmatic angle; (2) some alteration in form and size occurs with changes in position of the patient and the respiratory phase; (3) close association or adherence to the pericardium or pericardial fat pad; and (4) no significant change in size or shape over a period of years (except if there is an appreciable and sudden change due to an increase in secretion or resorption). Tomographic studies often elicit a distinct groove between the cyst and the diaphragm; if the cyst can be "separated" from the cardiac shadow, it may possibly be a cyst of the diaphragm.

The etiology of the cysts is also a moot question. Histologically, these cysts have flat endothelial cells which rest on a thin layer of collagenous fibers. These findings and the similarity of the fluid to that seen in

hygromas have led the authors to regard them as cystic lymphangiomas. Only those cysts, which have a stalk communicating with the pericardial sac, have a congenital origin and are considered true pericardial diverticula. A pericardial cyst may arise from persistent lacunae, which have united into one unicameral cyst; or, as a result of the budding-off from the so-called ventral-parietal recess of the pericardial sac; or, due to some abnormality in the development of the pleural cavity in which a variety of folds and obliterative phenomena occurs.

The differential diagnosis includes: (1) Hernia of the Larrey type (through the foramen of Morgagni). If a loop of intestine is contained in the hernial sac, the characteristic gas pattern will be observed. An omental hernia can be recognized by a wormlike network of fatty tissue anterior to the liver adjacent to the anterior abdominal wall. (2) Traumatic pericardial cysts may be diagnosed on the basis of a proper history. They contain liquified pericardial or parietal blood and are very well encapsulated. (3) Lipomata are more frequently found in the superior mediastinum. Their form is unchanged by alteration of position or phase of respiration. (4) Aneurysms of the aorta, heart or sinus of Valsalva require angiographic studies for a definitive diagnosis. (5) A pseudodiverticulum of the pericardium rests with a broad base on the pericardium and blends with the cardiac shadow. It has a wavy contour and usually shows adhesions to the pleura or mediastinum. The heart is frequently enlarged and/or decompensated. (6) Bronchial, thymic or teratoid cysts are most often located in the anterior-superior or middle mediastinum, otherwise they are similar to pericardial cysts roentgenologically.—7. Zausner, M.D.

Lukash, William M., Schneider, Paul J., and Sennett, Charles O. Angiosarcoma presenting as acute rheumatic pancarditis. *J.A.M.A.*, Sept. 13, 1965, 193, 975–976. (Address: Lt. Cdr. Lukash, MC, USN, U. S. Naval Hospital, Philadelphia, Pa. 19145.)

Primary cardiac tumors are rare and the total number now in the literature approaches 500.

This report is on a case of angiosarcoma in a young woman who presented acute rheumatic fever. The case history is detailed including the necropsy findings.

Pulmonary complications appeared to dominate the picture.—David C. Alfine, M.D.

Hunt, David D. Cervical spondylitis caused by Salmonella oranienburg. J. Bone & Joint Surg., Sept., 1965, 47-A, 1243-1246. (From: Division of Orthopedic Surgery, Stanford University School of Medicine, Palo Alto, Calif.)

A 67 year old woman noted spontaneous onset of neck pain. Five days later she experienced chills,

fever, and moderate diarrhea. Roentgenograms 3 weeks after the original episode showed extensive destruction of the fifth and sixth cervical vertebrae with collapse of the anterior portion of the fifth cervical vertebra. Physical examination revealed paracervical muscle tenderness but no limitation of motion. No mass was palpable. Barium swallow demonstrated slight soft-tissue prominence anterior to the region of bone destruction. Culture of cervical aspiration grew Salmonella oranienburg, occurrence of which is rare in North America. This is the first reported case of cervical spondylitis caused by Salmonella oranienburg.

Roentgenograms, taken 2 years after immobilization and antibiotic therapy had produced satisfactory results, showed healing of the lesions with slight sclerosis. There was residual irregularity and narrowing of the interspace between the fifth and sixth cervical vertebrae. Laboratory studies were normal.—Lois Cowan Collins, M.D.

HARDY, HARRIET L. Asbestos related disease. Am. J. M. Sc., Oct., 1965, 250, 381-389. (From: Massachusetts Institute of Technology, Massachusetts General Hospital, and Harvard Medical School, Boston, Mass.)

The author gives a short historical review of the problem of asbestosis and discusses 4 cases demonstrating varying severities of the disease. The increased use of asbestos in industry is noted as well as the experimental and epidemiologic evidence of its relation to chest tumors and pulmonary disease. With steadily increasing use of this material, the incidence of related disease can also be expected to increase.

Two tables on the important uses and the chemical composition of the 3 varieties of commercially used asbestos are given.—Donald S. Linton, Jr., M.D.

DEVITA, VINCENT T., TRUJILLO, NELSON P., BLACKMAN, ALDEN, H., and TICKTIN, HOWARD E. Pulmonary manifestations of primary hepatic carcinoma. Am. J. M. Sc., Oct., 1965, 250, 428-436. (From: The George Washington University, Medical Division, D. C. General Hospital, Washington, D. C.)

Primary carcinoma of the liver is not a rare disease, having been reported in 0.20-1.76 per cent of all necropsies. Extrahepatic metastases are common—up to 86 per cent. The association of primary hepatic carcinoma and cirrhosis is well documented.

The clinical presentation of this disease can be pleomorphic. Many authors have described its varied manifestations; however, the literature has not emphasized the pulmonary manifestations, especially roentgenologically.

The authors report 4 cases which present 3 different types of pulmonary lesions.

From their cases and a review of the literature, the following pulmonary changes, especially in association with cirrhosis of the liver, should bring to mind primary hepatic carcinoma: (1) elevation or bulges of the right hemidiaphragm; (2) a right pleural effusion; (3) a solitary pulmonary or mediastinal mass; (4) diffuse discrete pulmonary nodules; (5) pulmonary infarction; and (6) diffuse interstitial infiltration of the lungs.—W. J. Carmoney, Jr., M.D.

ABDOMEN

Good, C. Allen. Benign tumors of the stomach and duodenal bulb. The 1965 Gordon Richards Memorial Lecture. (Delivered at the Annual Meeting of the Canadian Association of Radiologists, Toronto, February 24–28, 1965.) J. Canad. A. Radiologists, June, 1965, 16, 92–104. (From: Section of Roentgenology, Mayo Clinic and Mayo Foundation, Rochester, Minn.)

This is an excellent comprehensive study on the subject and, if the complete detail is desired, it might be well to obtain a reprint from the author.

The author's conclusions are actually a very good abstract and I have taken the liberty to cite his conclusions almost *verbatim*: Benign tumors make up between 10 and 15 per cent of all tumors involving the stomach and duodenal bulb. Adenomatous polyps, leiomyomas, lipomas and heterotopic pancreatic tissue are the most common varieties.

Benign tumors are important because some show malignant changes histologically. Carcinoid is truly a malignant tumor. About 20 per cent of adenomatous polyps and 10 per cent of leiomyomas and neurinomas show evidence of malignant change.

Benign tumors are important also because they may ulcerate and bleed, or prolapse through the pylorus and cause symptoms of obstruction.

They may be divided into intraluminal, submucosal and subserosal categories, which may often be distinguished roentgenologically.

The roentgenologic manifestations suggesting benignancy were described 40 years ago by Moore. They are (a) sharply circumscribed filling defect, (b) rugal folds normal in the neighborhood of the tumor although flattened over it, and (c) pliant wall of the stomach with no disturbance of normal peristalsis.

Some clinical and roentgenologic features may aid in arriving at a specific diagnosis. (a) Multiple tumors are usually adenomas. (b) Achlorhydria is more common in association with adenomas. (c) Typical mucocutaneous pigment is found in Peutz-Jeghers' syndrome. (d) Some carcinoid tumors secrete serotonin and produce the clinical pattern of functioning carcinoid syndrome. (e) Deep pits or ulcers are suggestive of leiomyoma or neurinoma. (f) A dumbbell tumor is likely to be a leiomyoma. (g) A

lipoma may produce a more radiolucent appearance and may change shape as the peristaltic wave passes over it. (h) The dimple produced by the vestigial duct in heterotopic pancreatic tissue should suggest the proper diagnosis if there is no clinical evidence of ulceration and bleeding.

Recommended treatment can be summarized as follows: (1) It may be preferable to remove any tumor in order to make a histologic diagnosis. (2) A tumor larger than 2 cm. in diameter should be removed because of the increased chance of malignant change. (3) Excision is indicated if the tumor is ulcerated or if bleeding has occurred. (4) Removal is to be recommended if the tumor prolapses through the pylorus or if symptoms of obstruction are present. (5) If growth of the mass can be demonstrated by means of serial examinations, the tumor should be removed.—Peter C. Truog, M.D.

Shaw, Richard E. (Coventry, England.) Appendix calculi and acute appendicitis. *Brit. J. Surg.*, June, 1965, 52, 451-459.

The author states that stones are formed in the appendix with greater frequency than in either the gallbladder or the urinary tract, and indeed the appendix is probably the commonest site of stone formation in the body.

Roentgenographic examination of the appendix after removal in 240 cases shows an incidence of 33 per cent containing stones. Much confusion has been caused by the use of a variety of names for the same object—appendicolith, fecolith, coprolith, concretion, etc., and by attempts to distinguish between calcified and non-calcified bodies. The author makes a plea for discontinuing the term "fecolith" for non-calcified fecal masses. Such bodies are simply feces. The other calcium containing bodies are all stones in various stages of formation and may be termed "appendix calculi."

Appendix stones usually measure 2-3 cm. in diameter. They are round or oval in shape but when multiple may be faceted. In 10 per cent of cases of calculous appendicitis the stones are sufficiently calcified to show as laminated or ring shadows, usually situated in the right iliac fossa. Their position varies with the position of the appendix so that they may be found in other parts of the abdomen. If the appendix is not fixed by adhesions, the position of the shadows will vary from one film to another with changes in posture. When calculi are multiple, their densities lie in a straight or curved line and the pattern of a large proximal and several smaller distal stones is sometimes seen. In the acute case dilated loops of ileum may also be seen. In non-acute cases stones of a large size may be evacuated from the appendix into the cecum and in this way a self-cure may be achieved.

Although the incidence of stones is the same for different ages and both sexes, the existence of stones

is of great significance. There is a 35 per cent higher incidence of calculous appendicitis proceeding to gangrene and perforation than in the non-calculous form of appendicitis.—Richard C. Pfister, M.D.

Montori, A., and Zechini, F. La poliposi del grosso intestino: contributo anatomo-clinico. (Polyposis of the large intestine: anatomic clinical contribution.) *Ann. ital. di chir.*, 1965, 41, 1102-1155. (From: Istituto di Semeiotica Chirurgica dell'Università di Roma, Italy.)

The authors contribute an exhaustive review of the literature and a well documented study of 14

Definition. Polyps are defined as primary or tumoral and secondary or inflammatory. By common usage, the terms polyp and polyposis are synonymous with adenoma and adenomatosis. The lesion may present itself in the following forms:

- (1) Solitary polyp—sessile or pedunculated.
- (2) Multiple polyposis—the mucosa surrounding each polyp is normal.
 - (a) Segmental—affecting one segment of the large bowel.
 - (b) Disseminated—involving the entire large intestine.
- (3) Diffuse or familial polyposis—the mucosa of the colon and of the rectum is replaced by polypoid formations and no normal mucosa is recognizable.

Site. The preferential site is from 11-15 cm. from the anal orifice. The most frequent localization of juvenile adenomatosis is 4-6 cm. from the anus. It is held that familial polyposis has its origin in the rectum and its diffusion is retrograde, even to involvement of the small intestine.

Incidence. The determination of the true incidence of the disease is fraught with difficulty, principally because of the variability of the criteria used in statistical studies. Unquestionably the solitary polyp is the most frequently encountered. Multiple polyposis is second in frequency. The familial or diffuse form is a rare entity.

Age. Most authors maintain that the solitary polyp becomes evident principally in the fifth and sixth decades of life; however, 8.8 per cent have been reported in infants. According to Soulard et al. (1961) multiple polyposis occurs in 20 per cent of cases at all ages. The diffuse or familial type affects the young, exceptionally the infants.

Carcinomatous degeneration. According to many authors polyposis is to be considered a precancerous lesion. Others maintain that this concept is not always acceptable especially when referring to solitary and multiple adenomatosis.

Diagnosis. The most common symptoms are hemorrhage, diarrhea and abdominal pain. Diagnosis is

established by rectal exploration, sigmoidoscopy and barium enema study.

Conclusion. The authors conclude that polyposis of the large bowel is to be considered a precancerous pathologic process and that the treatment is surgical excision.—Anthony A. Blasi, M.D.

FERRANTE, WILLIAM A., and EGGER, JOHN. Toxic megacolon complicating chronic ulcerative colitis. South. M. J., Aug., 1965, 58, 969-973. (From: Departments of Gastroenterology and Colon and Rectal Surgery, Ochsner Clinic, New Orleans, La.)

Although toxic megacolon is rare, it is a serious complication which may terminate fatally in 20 to 50 per cent of cases in most series.

This dreaded complication of ulcerative colitis usually develops during an acute exacerbation of the disease in which the local picture of a dilated atonic colon is conjoined with the systemic picture of collapse, shock and sepsis. This is characterized by fever, diarrhea with or without blood, tachycardia, severe abdominal distention, prostration and ane mia.

On proctoscopic examination, evidence of ulcerative colitis is usually found, but the process in the rectosigmoid may or may not be as severe as in the more proximal colon. In some instances the rectum and sigmoid may be normal.

Plain roentgenograms of the abdomen demonstrate an extremely dilated colon, the transverse colon often being the site of pronounced dilatation. The cobble stone appearance of pseudopolyposis may be visualized if the disease has become chronic.

The authors believe that the basic etiologic factor in toxic megacolon is the rapid complete destruction of all layers of the bowel wall, especially the outer muscle layer and resultant severe dilatation of the colon. Other causes that have been suggested are myenteric plexus destruction, hypokalemia, corticosteroids, anticholinergics, various antibiotics and barium enema examination.

Early diagnosis of toxic megacolon is imperative because it warns of impending disintegration and perforation of the colon with fatal consequence. Intensive medical treatment is directed toward preparing the patient for early surgery. This is continued as long as improvement continues. If, however, the patient's condition deteriorates with medical management, emergency surgery is indicated. Although others have suggested cecostomy, ileostomy and delayed colectomy, the authors prefer subtotal colectomy and ileostomy. The rectum is removed at a later date. No fatalities occurred in their series of 6 cases treated in this manner.—Richard C. Pfister, M.D.

STAAB, EDWARD V., and VIX, VERNON A. Serum glutamic oxalacetic transaminase

levels following tannic acid enemas. Radiology, June, 1965, 84, 1087–1089. (Address: Radiology Service, Minneapolis Veterans Hospital, 54th Street and 48th Avenue South, Minneapolis, Minn.)

Tannic acid has been added to barium sulfate for evaluation of the colon and distal small bowel by radiologists for years. More recently it has been combined with the cleansing enemas given prior to the barium enema examinations. Several groups have recently presented suggestive evidence to implicate this practice as a factor in some deaths due to liver toxicity.

Tannic acid toxicity to the liver in the concentrations studied along with the ability of this substance to be absorbed from a variety of areas seems well established. The problem in man is primarily whether or not this substance is absorbed from the bowel in sufficient amounts to produce toxicity.

Because the authors were using tannic acid regularly in their colon examinations, they undertook this study to evaluate the possible frequency of hepatic toxicity in the past and to aid in a decision as to its possible future use. Serial serum glutamic oxalacetic transaminase (SGOT) determinations were employed for evaluation of liver injury. SGOT has been shown to be a sensitive indicator of hepatocellular damage in man. The SGOT determinations in this study were obtained with an automated version of the Reitman and Frankel colorimetric method. In patients who were to undergo a barium enema examination, blood samples were taken to determine the SGOT 6 hours before and 18 and 36 hours after the procedure. The barium enemas were administered in the routine manner with a Bardex catheter when necessary and an attempt was made to fill the terminal small bowel. All of the patients were males. A barium sulfate mixture that contained 0.25 per cent tannic acid was used. Tannic acid was not used in the cleansing enemas.

In 2 of 94 patients studied, the serial SGOT determinations showed changes. One was a borderline change in a 71 year old male with regional ileitis of the terminal small bowel. The other was a definite change in a 68 year old poorly controlled diabetic which, in view of a changing ECG pattern, was probably the result of coronary artery disease and myocardial injury. A repeat study in this case I month later produced no change in the SGOT level.

None of the other 92 patients showed any change. It is concluded that although no significant hepatic toxicity was found in this study, higher concentrations of tannic acid might produce other results.—

Paul M. Kroening, M.D.

Lust, Franz J. Roentgenologic manifestations of gastric and duodenal ulcers in children. *Pediat. Clin. North America*, May, 1965, 12, 411–421. (Address: 17 East 89th Street, New York, N. Y.)

Practical and thoughtful suggestions are offered to offset some of the problems which confront roentgen examination of the gastrointestinal tract in children. Since many youngsters are afraid of dark rooms, it is recommended that roentgenography be the initial procedure and that fluoroscopy follow. By this time the child's apprehensions are likely to be assuaged. Complete darkening of the fluoroscopic room is not essential; the shadow on the fluoroscopic screen is sufficiently clear to be visible even with the examining room door ajar. A small amount of light can convert a rebellious patient to a cooperative one. Flavoring the contrast medium and, above all, patience are factors that contribute to a more pleasant and adequate examination.

Concomitant functional abnormalities may aid in the diagnosis of ulcer. Gastric secretion can be measured by placing some of the contrast medium into a test tube when the patient drinks his prescribed amount, and roentgenographing the test tube on the same film as the stomach (upright) 20 minutes later. The normal degree of sedimentation is thus available for comparison with the degree of sedimentation demonstrated in the stomach. The layer of fluid overlying the barium in the stomach usually represents the hypersecretion which has occurred after ingestion of barium. Pylorospasm and decreased peristalsis may be absent initially, but occur after an interval of 1 to several hours.

In children, gastric ulcers occur on the lesser curvature of the stomach, mostly in the mid-portion. Roentgenologically, the ulcer presents as a smoothedged, shallow crater. Niches, craters, and constant deformity of the duodenal cap are typical of ulcer in this organ. The duodenal cap is small in children and has rapid motility, making it necessary to take spot roentgenograms in various positions in addition to fluoroscopy.

Proper therapy requires recognition of all organic and functional changes of the digestive tract.— Lois Cowan Collins, M.D.

BOLEY, SCOTT J., KRIEGER, HARVEY, SCHULTZ, LEON, ROBINSON, KENNETH, SIEW, FRED P., ALLEN, ARTHUR C., and SCHWARTZ, SOLOMON. Experimental aspects of peripheral vascular occlusion of the intestine. Surg., Gynec. & Obst., Oct., 1965, 121, 789-794. (From: Departments of Surgery, Radiology, and Pathology, Jewish Hospital of Brooklyn, Brooklyn, N. Y.)

The vascular origin of many disorders of the intestines has become a subject of renewed interest over the past several years and the roentgenographic features of reversible vascular occlusion of the colon, as well as other disorders have been described.

Many conditions other than primary vascular disorders may compromise the blood supply of the normal intestine but the clinical manifestations are similar or identical. These changes are dependent on the availability of collateral blood flow rather than on the nature of the parent disease.

To study the effect of varying degrees of vascular occlusion, the authors utilized the technique of injecting glass and ceramic microspheres, ranging from 35 to 100 microns in diameter, into the mesenteric arteries of mongrel dogs by selective aortic catheterization and direct injection. A spectrum of pathologic changes ranging from minimal mucosal edema to rapid intestinal dissolution was produced. In general, the larger the quantity of spheres and the smaller their size the greater was the damage. This experimental obstruction of vessels on and within the walls of the colon and small intestine resulted in pathologic changes ranging from superficial mucosal ulceration to total necrosis. These changes are identical to those seen in the human intestine with demonstrable small vessel disease.

Attention has been directed recently to a possible association between the ingestion of enteric-coated thiazides with potassium, and circumferential stenosing ulcers of the small bowel. Experimental work by the authors suggests that potassium chloride absorption in high concentration produces venous spasm or paralysis, stasis, and subsequent segmental infarction. The clinical and pathologic changes produced in these experiments closely resemble the gross appearance of necrotizing colitis and acute segmental ulcerative colitis in man.

A reversible form of vascular occlusion of the colon has also been produced and the submucosal hemorrhages 24 hours after injection, the superficial ulcerations 48 to 72 hours after injection, and the complete healing after 2 weeks corroborate the clinical evidence that this condition may be a late result of vascular accidents in the large intestine.

The authors conclude that a relationship between these experimentally produced changes and the clinical entities mentioned may exist.—James R. Knapp, M.D.

WHOLEY, MARK H., BRON, KLAUS M., and HALLER, JORDAN D. Selective angiography of the colon. S. Clin. North America, Oct., 1965, 45, 1283–1291. (From: Departments of Radiology and Surgery, University of Pittsburgh and Veterans Administration Hospitals, Pittsburgh, Pa.)

The value of visceral angiography is now established and by means of the percutaneous technique introduced by Seldinger in 1953, the arteries of all of the major abdominal viscera can be selectively catheterized. The colon has a dual blood supply, receiving blood via both superior and inferior mesenteric arteries. Therefore, in studying the colon, both vessels must be catheterized.

The indications for, and the value of, selective angiography of the colon have not been clearly defined. Arteriography can demonstrate the location and size of a lesion and may in addition indicate its extraluminal extent. It has been useful in locating vascular lesions such as hemangioma, arteriovenous malformations, etc. It may be useful in studying cases with gastrointestinal bleeding of unknown etiology.—Richard E. Kinzer, M.D.

Solomon, Solomon S., Moran, John M., and Nabseth, Donald C. Villous adenoma of rectosigmoid accompanied by electrolyte depletion. J.A.M.A., Oct. 4, 1965, 194, 5-10. (From: Tufts Medical and Surgical Services of Boston City Hospital, Boston, Mass.)

Villous adenoma of the colon may cause a profuse watery discharge and 34 cases have been reported since 1954 in which symptomatic fluid and electrolyte depletion resulted from such a tumor.

The authors add 2 more cases and present a discussion of current management and the serious nature of this condition. Watery diarrhea, extreme weakness, dehydration and renal insufficiency are almost constant findings but a variety of bizarre accompanying symptoms frequently accounts for delayed or erroneous diagnosis. Because of the soft texture and mobility of these tumors, they may be difficult to see or palpate on physical examination. Of the authors' 2 cases, I had probably been missed on a physical examination 3 years earlier and the other was found at autopsy.

The mean age in all 36 reported cases is 64 years and the mean duration of symptoms 4.2 years. Rectal losses are hypertonic with respect to potassium and hypokalemic nephropathy is probably the basis of renal insufficiency in this condition.

Surgery is the accepted method of treatment for villous tumors of the colon. In this group of 36 patients the 6 who had fulguration or a local excision required further surgery and 4 of these had a malignancy which was first found at the time of the subsequent resection. There is no known histologic difference between villous adenomas that cause a fluid and electrolyte depletion and those that do not. Eighty per cent of villous adenomas of the colon are found in the rectosigmoid and many entirely encircle the rectum. Invasive carcinoma occurs in 25 per cent of the cases.

The authors feel that adequate biopsy is difficult and because of the tendency of these secreting tumors to recur following inadequate excision or fulguration, an appropriate cancer operation should be performed at the outset, providing the patient is able to withstand surgery.—James R. Knapp, M.D.

BLEIFELD, W., and EFFERT, S. The demonstration of hydatid cysts in the liver by the supersonic-echo technique. German Med. Monthly, June, 1965, 10, 240–242. (From: First Medical Clinic, Medical Academy, Düsseldorf, Germany.)

The diagnostic application of ultrasound depends on the special physical properties of this form of energy; a homogeneous medium is traversed by supersonic waves at a specific velocity. When the supersonic impulses reach an interface between two media of different acoustic properties, a portion of their energy enters the second medium and a portion is reflected.

The source is a piezo-electric device consisting of a small disk of barium titanate crystal which contracts and expands depending on direction and with the same frequency of the alternating current it is subjected to. The fluctuations in thickness thus produced are transmitted as supersonic waves into the adjacent medium, which when reflected in turn also produce their own variations in thickness of the crystal. This echo of ultrasonic waves produces electrical changes at the surface of the crystal which can be amplified and transmitted to a cathode-ray oscilloscope for recording. This procedure has been useful to record position and movement of intracardiac structures and less useful in diagnosis of solid tumors.

The authors report a case to show that cysts in the liver can be demonstrated safely and directly by this technique. A 45 year old male had noted right upper quadrant swelling. He had undergone partial hepatic resection for "tumor" in 1958 in Greece. Physical examination revealed the liver enlarged down to the right iliac crest with 4 cystic areas at the lower margin.

The authors discuss the supersonic echogram of normal liver and that produced over a cyst in the liver. Distinct markings indicating the anterior and posterior walls of the cyst made it possible to measure the size of the cyst, and in I instance recorded a multilocular cyst. The diagnosis of hydatid cysts was confirmed by serology and histology following surgical removal. Postoperative echograms revealed normal liver.

This simple safe technique may be employed to demonstrate hollow spaces filled with fluid; i.e., various types of cysts and abscesses and even intrauterine fetal biparietal skull measurements as reported by other workers.—John Truksa, M.D.

FONKALSRUD, ERIC W., and BOLES, E. THOMAS, JR. Choledochal cysts in infancy and childhood. Surg., Gynec. & Obst., Oct., 1965, 121, 733-742. (From: Department of Surgery, The Ohio State University, and the Children's Hospital Research Foundation Columbus, Ohio.)

The authors report a total of 7 patients with choledochal cysts treated in the 10 year period, 1953-1963. Four patients were infants varying in age from 4 to 12 weeks and 3 patients were older children ranging in age from 4 to 8 years. In the infants, clinical symptoms indistinguishable from obstructive

jaundice due to biliary atresia were noted. Specifically, the infants had jaundice accompanied by acholic stools, with no apparent abdominal pain and no palpable abdominal mass. In contradistinction to the infants, 2 of the older children had the typical clinical triad of pain, jaundice and abdominal mass. The other child presented with the uncommon complication of hematemesis due to portal hypertension, a presentation that has been previously described in the literature. All of these patients were ultimately treated with internal drainage procedures and have survived for periods of 3 to 10 years postoperatively without significant clinical symptomatology or signs.

It appears that symptomatology remains the most helpful diagnostic aid in this condition, since neither laboratory nor roentgenologic studies have proved to be of consistent value. When all age groups are considered, the classic manifestations of jaundice, abdominal pain, and abdominal mass are found in 60 to 70 per cent of the cases. However, this symptom complex most definitely does not apply to the infant in whom obstructive jaundice has been the presenting problem. In the infant situation, the approach to diagnosis has been exploratory laparotomy and if possible operative cholangiography through the gall-bladder. This procedure will demonstrate a choledochal cyst if one is present.

In the older children when the diagnosis is seriously considered, roentgenologic studies can be of specific diagnostic assistance. Plain roentgenograms are usually not helpful but may show a mass contiguous with the liver and displacement of adjacent gas-containing gastrointestinal viscera. The single most useful procedure is the upper gastrointestinal series. It will often demonstrate displacement of the duodenum anteriorly and to the left. Oral cholecystography has not been of help because the common duct does not concentrate the contrast medium and therefore can rarely be visualized. If the serum bilirubin is normal, the intravenous cholangiogram may be diagnostically specific. In the situation where there is portal hypertension with bleeding esophageal varices, splenoportography is of particular value. The splenoportogram obtained in the case referred to in this series was unsatisfactory but may have shown displacement of the portal vein and perhaps some degree of obstruction which would have been helpful in giving a clue to the diagnosis prior to laparotomy. Operative cholangiograms are certainly of help in confirming the diagnosis and also in demonstrating the type of choledochal cyst. One patient in the series had a diverticulum type of choledochal cyst, while all of the other patients showed the more common cystic dilatation of the common bile duct. Roentgenographic examinations, particularly the upper gastrointestinal series, are of value in follow-up on these patients after operation.

The safest and most effective method of treatment is internal drainage of the cyst by anastomosis to the intestinal tract. The policy of the authors is to do a side to side cystoduodenostomy as the procedure of choice. In the case of recurrence of symptoms or of development of significant cholangitis, reconstruction of the anastomosis using the Roux-en-Y technique would be in order.—Lionel W. Young, M.D.

HERMANN, ROBERT E., and HOERR, STANLEY O. The value of the routine use of operative cholangiography. Surg., Gynec. & Obst., Nov., 1965, 121, 1015–1020. (From: Department of General Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio.)

The authors advocate the use of routine operative cholangiography for operations on the gallbladder, bile ducts and pancreas. They state that accuracy, proficiency and speed are developed by frequent use, and with the operative cholangiogram as a guide for the need of open exploration of the common bile duct, unnecessary duct explorations are avoided. In addition, unsuspected stones in normal bile ducts are identified.

A detailed explanation and several illustrations of the various techniques available are included as well as roentgenographic reproductions.—Donald S. Linton, Jr., M.D.

GENITOURINARY SYSTEM

Boesch, Dieter. Erfahrungen mit Conray bei der intravenösen Urographie in der ambulanten Praxis. (Experiences with conray in intravenous urography of ambulatory patients.) Röntgen Blätter, July, 1965, 18, 315-322. (Address: Röntgen-Institut der Allg. Ortskrankenkasse für den Stadtkreis Bielefeld, Oelmühlenstr. 57, Bielefeld, Germany.)

Conray, new contrast medium for intravenous urography, is available in three concentrations: conray 60, conray 70 and conray 80. Conray 60, representing the lowest concentration, is used in children and asthenic, debilitated patients, conray 70 is the medium of choice in the average normal patient and conray 80, also known as angioconray, is reserved for very obese people.

Most contrast media cause unpleasant side effects, mainly due to iodine toxicity, and are therefore not well tolerated by ambulatory patients. Conray is the least toxic, causing only occasionally mild and transient side effects. It is rapidly eliminated and its effect on the blood pressure is only minimal and very transient.

The new medium was used in 200 consecutive ambulatory patients. It was preceded by an intravenous test dose of 1 cc. Thereafter, an average dose of 20 cc. was injected in adults and slightly less in children and debilitated patients. Roentgenograms were made 7 and 12 minutes after the injection while

abdominal compression was applied. A 17-minute roentgenogram was obtained after release of the compression.

Minimal side effects were noted in only 12 patients, lasting less than 1 minute, and there was no veno-spasm. A low viscosity permitted a more rapid injection than with other media. The contrast was sharp and strong, especially when conray 80 was used. Conray proved to be the urographic medium of choice in an ambulatory praxis.—Ernest Kraft, M.D.

MacEwan, D. W. Improved detail in excretory urography using twice the amount of contrast agent. J. Canad. A. Radiologists, June, 1965, 16, 105-113. (From: The Montreal General Hospital, Montreal, Quebec, Canada.)

From December 1, 1963 until December 1, 1964, 2,964 patients were examined by excretory urography using 50 cc. of material (60 per cent renografin)—twice as much as usually recommended. There was a definite impression that the detail of the kidneys, ureters and bladder was considerably better.

In this same year, 334 patients were examined who had had earlier urograms using conventional dosages and who also had the same renal function at the time of the urographies. The examinations made using twice the amount of contrast material were compared with the earlier studies and were graded: good gain, slight gain, no change and worse. Sixteen patients were excluded from the study because their renal function was different at the time of one of the examinations, and a further 25 patients were rejected because striking structural changes had occurred between the two examinations, e.g., operations upon the kidneys, ureters and bladder or the construction of ileal loop conduits.

The general summary showed 60 per cent with a good gain, 25 per cent with a slight gain, 17 per cent with no change, and 2 per cent worse. The author states that there was no evidence of increased toxicity to the increased dose.—Peter C. Truog, M.D.

SARRE, H., SIEBERTH, H., and NOLTENIUS, H. Goodpasture's syndrome: glomerulonephritis and pulmonary hemorrhage. German Med. Monthly, July, 1965, 10, 280-284. (Address: Prof. Dr. H. Sarre, Medizinsche Universitäts-Poliklinik, Hermann-Herder Str. 6, Freiburg i. Br., Germany.)

Goodpasture first described the syndrome named after him in an 18 year old boy who fell ill during an influenza pandemic in 1919. Before 1948 no further accounts of this disease were published. Since then, 41 additional cases have been reported. This syndrome consists of a rapidly ratal disease with characteristic symptoms. Its mean duration is 5 months, and only 1 case is on record as lasting more than 1 year. Ninety per cent of all patients are men, and in

85 per cent the disease occurs before the age of 30.

The first sign is usually stated to be hemoptysis, which may be massive or marely take the form of

which may be massive or merely take the form of blood-tinged sputum. At the same time, or sometimes earlier, there is sudden onset of pronounced weakness, fatigue and exhaustion. Other symptoms which may occur are headaches, sore throat, dyspnea, predominantly facial edema, perspiration, anorexia, vomiting and fever. Roentgenologically, bilateral diffuse infiltrates are usually seen which are fully reversible. Later, renal insufficiency predominates. The urine is characterized from the very beginning by considerable proteinuria. Within a few weeks or months, renal failure associated with oliguria and uremia ensues. At present only supportive treatment can be given, which includes blood transfusions, hemostatic drugs and dialysis. Extracorporeal or peritoneal dialysis, as performed in 4 patients thus far, has prolonged life for only short periods.

Goodpasture's syndrome should be considered as a diagnostic possibility when the following signs occur simultaneously: (1) Hemoptysis; (2) nonspecific bilateral infiltrates in the middle or lower lobes, or in both; (3) pronounced proteinuria; and (4) severe hypochromic anemia.

A detailed discussion of pathology and pathogenesis is included.—Douglas S. Kellogg, M.D.

TAKARO, TIMOTHY. Experimental renal angiography. Surg., Gynec. & Obst., Sept., 1965, 121, 579–584. (From: Research Service, Veterans Administration Hospital, Oteen, N. C.)

Direct magnification in experimental renal angiography requires low milliamperage because of the fine focal spot utilized. For adequate visualization of the interlobular and arcuate arteries allowed by this technique, long exposures are necessary. Suprarenal aortic occlusion using an inflated indwelling balloon, to slow renal circulation, was studied as a means of facilitating a long exposure time. The complications of vascular stasis were studied using one of the most toxic contrast materials, sodium acetrizoate 70 per cent, as compared with a more innocuous material, sodium iodothalamate 66.8 per cent. Toxicity was measured by the presence or absence of seizures, paralysis and blood urea nitrogen elevation, related to injection, and in some with I'm renograms before and after injection of contrast material.

One hundred and one mongrel dogs were divided into a control group receiving sodium acetrizoate 70 per cent, and 5 groups receiving low molecular weight dextran, dextrose, mannitol, saline, and urea prior to sodium acetrizoate 70 per cent. The seventh group received sodium iodothalamate preceded by mannitol. In each group, aortic occlusion was used in about one half of the animals.

In most control animals, convulsions occurred immediately. Lesser neurologic manifestations were seen in the premedicated groups, and only after release of the occluding balloon. Arcuate and/or interlobular artery opacification was good in 43 per cent using aortic occlusion, and only 20 per cent without occlusion. Preliminary osmotic diuretic infusion seemed necessary for clear-cut delineation of interlobular arteries. The greatest protection against both nephrotoxic and neurotoxic effects of sodium acetrizoate was afforded by mannitol and dextrose; the least by normal saline and urea. Nephrotoxicity, as measured by I¹³¹ renography and postmortem studies of the kidneys, was striking after acetrizoate, apparently unrelated to aortic occlusion, but with some protection using preliminary diuretics. Minimal or no changes were seen using iodothalamate.

The mechanism of toxicity of contrast media has been studied extensively, and some feel that intravascular aggregation of red cells due to hypertonicity or hypercomolarity of the contrast media is the important toxic factor, while others feel a direct vascular toxic effect to be present. Perhaps the osmotic diuretics increase blood volume sufficiently to force the aggregates through damaged but distended vessels; they may also act by increasing protein debris washout from the collecting tubules.

A significantly lower incidence of convulsions was seen in animals where aortic occlusion was used. In explanation, it is suggested that lumbar arterial blood flow direction is reversed below the occlusion because of collateral flow above, thereby providing protection for the spinal cord during injection.—

Mark D. Reiss, M.D.

DECK, M. D. F. Medullary sponge kidney with renal tubular acidosis: a report of 3 cases. J. Urol., Oct., 1965, 94, 330-335. (From: Department of Diagnostic Radiology, Sydney Hospital, Sydney, New South Wales, Australia.)

Medullary sponge kidney and renal tubular acidosis are two uncommon conditions affecting the kidneys.

The author reports 3 cases in which the combination of the two conditions was present. In all 3 cases, there was a family incidence of renal tubular acidosis.

In Case 1, a 21 year old female, the patient's father was known to have this disease. Roentgenographic examination of her kidneys showed numerous calculi in the renal pyramids associated with multiple small cysts involving the collecting system chiefly in the region of the tubules and canaliculi. Laboratory tests revealed an inability to concentrate the urine, and there was hyperchloremic acidosis with hypokalemia. There was inability to acidify the urine with a lowered excretion of hydrogen ions and ammonium ions.

Cases II and III were mother and daughter both exhibiting roentgenographic evidence of medullary sponge kidney with numerous calculi and cystic lesions throughout the renal pyramids. Both of

these patients also exhibited the laboratory findings of inability to acidify the urine and a reduction in the excretion of hydrogen ions and ammonium ions.

In a discussion of the etiology of the combined diseases, the author indicates that while renal tubular acidosis may be, and frequently is, the result of pyelonephritis, a well-established complication of medullary sponge kidney; the other possibility is that the renal tubular acidosis is the primary defect and that subsequent development of medullary sponge deformity is the result of the formation of calculi and their extrusion into the renal excretory passages. Evidence in favor of this is the familial incidence of the combined disease as noted in the 3 cases.

The author illustrates this article with 2 tables showing the biochemical and renal function tests and with 3 composite figures of the pyelograms in each individual case.—George W. Chamberlin, M.D.

NEAL, M. PINSON, JR., HOWELL, TALMADGE R., and LESTER, RICHARD G. Contrast infusion nephropyelography. J.A.M.A., Sept. 20, 1965, 193, 1017–1020. (Address: Dr. Neal, 1200 E. Broad Street, Richmond 19, Va.)

In recent years, investigators have developed nephrotomography and advocated the use of large volumes of contrast material to enhance intravenous pyelography. The authors report in detail their drip infusion nephropyelography method.

The patient is prepared in the usual manner with the exception that fluids are not restricted. A standard scout roentgenogram of the abdomen supplemented with scout laminagrams is obtained. Using sodium diatrizoate (hypaque), in dosage according to the patient's weight, mixed with an equal quantity of sterile distilled water, the authors rapidly infuse this solution into the patient via an 18 gauge needle within 5 minutes. At the end of the infusion, 1 cm. laminagrams are taken at the predetermined levels. Afterwards, routine 10, 20, and 30 minute roentgenograms are obtained. In hypertensive patients minute sequence laminagrams are taken at $\frac{1}{2}$, 2, 3, 4, and 5 minutes from the beginning of the infusion.

In a series of 55 patients, ranging from 5 months to 84 years in age, with a mean age of 54 years, 48 studies were definitely contributory to a roent-genologic diagnosis, especially in 20 patients who previously had had suboptimal intravenous pyelograms. Eleven patients with suspected renal mass lesions were examined. The authors state that a renal mass of 2 cm. or larger can be correctly diagnosed without further procedures.

This technique is useful in renal mass lesions, hypertension, renal vascular impairment, "the unsatisfactory pyelogram," renal failure, congenital urinary anomalies, ureteral visualization, cystography or urethrography, and total organ opacification.

With minimal preparation and no dehydration,

this is a simple, safe procedure that may be accomplished in any x-ray department or office.—W. J. Carmoney, Jr., M.D.

FELDMAN, MERRILL I., COADE, WILLIAM J., and SEIFE, IRWIN. Large volume contrast nephrotomography. J. Urol., Aug., 1965, 94, 196–198. (From: Department of Radiology, Lynn Hospital, Lynn, Mass.)

Indications for large volume contrast nephrotomography include those patients who have an abnormal routine excretory urogram suggestive of an intrarenal mass or calyceal deformity, an indeterminate pyelogram in the presence of unexplained hematuria and azotemia, and as a substitute for retrograde pyelography.

The authors recommend the use of 125 cc. of renovist with 125 cc. of isotonic saline solution given intravenously over a period of 10 minutes. The usual tomograms are made at the appropriate levels 10 minutes after completion of the infusion; satisfactory nephrograms may be obtained for as long as 30 minutes thereafter. The follow-up routine pyelographic studies which may be obtained at the same time will usually show complete contrast opacification of the renal cortex, collecting systems, ureters, and bladder. The quality of visualization is at least equal to or superior to that of retrograde pyelography.

In a series of 30 cases not a single systemic reaction or other untoward effect has been encountered. It is the impression of the authors that patients tolerate the dilute contrast infusion better than the conventional small dose injection for the routine excretory urography.

Three composite figures are used to illustrate the value of this method.—George W. Chamberlin, M.D.

Porstmann, W., Wierny, L., and Munster, W. Pre-operative pressure measurements in stenosed renal arteries. *German Med. Monthly*, June, 1965, 10, 245-249. (From: Cardiological Unit, Charité, Berlin, Germany.)

The author describes a method of determining renal artery pressure gradients proximal and distal to areas of renal artery stenosis at the time of arteriography. A "significant" renal artery pressure gradient could be demonstrated pre-operatively by introduction of a filiform catheter through an Ödman catheter into the renal artery distal to the stenotic area and then taking alternate renal artery and aortic pressure readings.

Eleven cases are reported.—Edward M. Cockerill,

COPESTAKE, G. G. Renal arteriography: comparison of methods. J. Urol., Oct., 1965, 94,

846-488. (From: University of Western Ontario and Victoria Hospital, London, Ontario, Canada.)

In this article, the author compares and evaluates translumbar arteriography as performed by the surgeon with percutaneous transfemoral catheterization for the demonstration of the renal arteries by the radiologist. Thirty-eight procedures carried out by surgeons are compared with 51 individual procedures carried out by radiologists. Indications for the examinations included suspected tumors and cysts and cases of hypertension in which there was some evidence of impaired renal function which might be attributed to renal artery disease.

The results were tabulated as good, adequate, and nondiagnostic. It is shown that 39.5 per cent of the renal arteriograms made by surgeons were not of diagnostic quality as opposed to 19.6 per cent made by the radiologists. In 60.5 per cent of the surgical cases, some diagnostic information was obtained but only 23.7 per cent could be labelled "good." In the radiologic group, 80.4 per cent were readable but 60.8 per cent were considered good. Of the combined series, 45 per cent were considered good and 28 per cent were of no value whatever.

The study revealed that the radiologist took a longer time and used more film and more exposure to the patient than did the surgeon. Complications due to the deposit of contrast medium in the vessel wall were 34.2 per cent for the surgeon and 19.6 per cent for the radiologist.

In the author's experience, damage to the walls of the arteries by any method of intra-arterial injection is extremely common. With greater awareness of this danger and with a more critical review of the present series of examinations, a larger number of incidences of arterial wall damage has been revealed, particularly damage to the intimal layer.

It is emphasized that by any method, renal arteriography includes difficulties which have been underrated and complications which have not yet been fully uncovered.—George W. Chamberlin, M.D.

DOCKRAY, KARL THORD. Perirenal contrast medium: a new roentgenographic sign of neonatal urinary ascites. J.A.M.A., Sept. 27, 1965, 193, 1121–1123. (Address: 1810 19th Street, Lubbock, Texas.)

The purpose of this communication is to call attention to the diagnosis of neonatal ascites as a result of obstructive uropathy. Specific attention is given to a distinctive roentgenographic manifestation, the "halo sign." This name is derived from the appearance of a halo-like radiodensity around the kidney during excretory urography. The author reports a case of a 10 day old moribund boy who had severe respiratory distress in addition to ascites. No cardiac abnormality or peripheral edema was noted and

emergency laparotomy showed the presence of straw colored fluid in the peritoneal cavity without evidence of intestinal obstruction. Excretory urography performed postoperatively showed the halo sign in addition to moderate ectasia of the left pelvocalyceal system and bilateral hydroureter. The latter findings were best seen in roentgenograms taken 3 to 6 hours after injection. Subsequent re-exploration confirmed the presence of a collection of clear yellow fluid in the retroperitoneal compartment about the involved kidney. No evidence of gross communication between the renal collecting systems and the retroperitoneal area or the peritoneal cavity was discovered. Posterior urethral valves were later demonstrated. The infant was treated by decompression of the upper urinary tract, by insertion of a Penrose drain into the right retroperitoneal space and creation of bilateral nephrostomies. There was subsequent resection of the posterior urethral valves. He has survived 3½ years post surgery. He is thought to be the seventh survivor of this disorder.

The author surveyed the literature and found 6 of 9 surviving ascitic neonates who were noted to have an accumulation of intraperitoneal fluid associated with obstructive uropathy. He points out that transudation or extravasation of opacified urine from the kidney into the retroperitoneal space appears to be a plausible explanation for the roentgenographically demonstrated perirenal halo. Specific explanation of the mechanism of development of intraperitoneal fluid in association with the retroperitoneal extravasation is not made.—Lionel W. Young, M.D.

GEORAS, M. C., CHUN, J. YOUL, DINAN, J. J., and BECK, I. T. Islet-cell carcinoma (Zollinger-Ellison syndrome) with fulminating adrenocortical hyperfunction and hypokalemia. *Canad. M. A. J.*, July 24, 1965, 93, 137–143. (From: Department of Medicine and Department of Surgery, St. Mary's Memorial Hospital, and Department of Medicine, McGill University, Montreal, Quebec, Canada.)

The authors discuss the pathophysiology and clinical and laboratory features of Cushing's syndrome associated with islet cell carcinoma (Zollinger-Ellison syndrome), and report the sixth case of adrenal cortical hyperfunction found in association with a "non-functioning" islet cell carcinoma. They reviewed the literature and list the 15 sites of carcinomata, unrelated to pituitary or adrenal cortex, reported to cause hypercorticism. These tumors autonomously produce a polyseptide similar to ACTH, leading to the adreno-cortical hyperfunction. The predominant clinical symptoms of muscle wasting, generalized weakness, and thirst are rapid in onset. The classic clinical signs of Cushing's syndrome were lacking in about one-third of reported cases—a finding attributed to the rapid development of the process preventing the full-blown picture to develop, and the weight loss due to the primary tumor reducing the appearance of the Cushinoid obesity. Even though the clinical evidence of Cushing's syndrome is lacking, these cases commonly have extremely high levels of corticosteroids in blood and urine.

Hypokalemic alkalosis, a relatively rare finding in uncomplicated Cushing's syndrome, is quite frequent in the syndrome associated with neoplasm and may even be fatal. Unlike the hypokalemia reported in the Zollinger-Ellison syndrome with intractable diarrhea and low urinary loss of potassium, the case reported by the authors had profound urinary loss of potassium unresponsive to intensive intravenous therapy. The case described had a relatively long history of islet cell carcinoma with ulcerogenic diathesis, and in view of increasing evidence that ulcerogenic tumors of the pancreas produce a gastrin-like substance, the authors raised the possibility that two hormone-like substances were produced in their patient by the same primary neoplasm and/or its metastases.— Gary Tolley, M.D.

Hamilton, James P., and Koop, C. Everett. Ganglioneuromas in children. Surg., Gynec. & Obst., Oct., 1965, 121, 803-812. (From: Surgical Clinic of The Children's Hospital of Philadelphia and the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania, Philadelphia, Pa.)

The authors report a long term follow-up investigation of ganglioneuroma in 17 children. Ganglioneuromas represent the fully differentiated lesions which make up the benign end of the spectrum of tumors of sympathetic ganglia. At the other end of the spectrum is the malignant, undifferentiated neuroblastoma. The in-between group of partially undifferentiated tumors is referred to as ganglioneuroblastoma. Much diagnostic confusion arises in the middle group. Ganglioneuromas are classified as being peripheral when they involve the sympathetic ganglia and classified as central when they originate from sympathetic ganglia inside the sympathetic nervous system.

Ganglioneuromas are usually discovered incidental to some other ailment or on a routine physical examination. This was true in 12 of the 17 patients reported.

Roentgenographically, neurogenic tumors are the most common neoplasms in the posterior mediastinum in children. Ganglioneuromas are often seen as round or oval masses in the paravertebral gutters. Calcification within the tumor is commonly present and may assume any form. Its presence in neurogenic tumors indicates the end stage of a mass that is growing faster than its blood supply with subsequent necrosis and calcification. To the authors, calcification has no significance in differentiating malignant

from benign tumors. When calcification is present it is a help in differentiating neurogenic tumors from other posterior mediastinal masses such as duplications of the foregut or neuroenteric or bronchogenic cysts. Quite frequently costal deformities accompany the thoracic ganglioneuromas in the form of horizontal flattening, increased density and contour irregularities of the ribs. Some spreading-apart of the ribs, usually at their junction at the vertebrae, is also seen. When present in the abdomen, neurogenic tumors must be differentiated from nephroblastomas. The presence of the neurogenic tumor intraabdominally is usually manifested by some extrinsic distortion of the kidney or ureter with less evidence of intrinsic distortion than is seen with nephroblastoma. Inferior vena cavography is of value particularly in differentiating the benign neurogenic tumors from the malignant ones. The latter usually show evidence of vena caval obstruction (up to 90 per cent as reported by Allen and associates).

The urine concentration of vanilmandelic acid has been shown to be elevated both by neuroblastoma and ganglioneuroma. The determination is of value in distinguishing neurogenic tumor from other neoplasms.

Four of the 17 patients reported had in their case histories evidence of histologically verified malignant neuroblastoma with subsequent histology indicating ganglioneuroma. It is pointed out that tumors of neural crest origin have been assumed to have the propensity to "mature" from malignant neuroblastomas into benign ganglioneuromas. The authors indicate that it may be reasonable to assume that all neural crest tumors start out as neuroblastomas and with time some of them mature into ganglioneuromas. The changing of a malignant tumor into a benign one may represent maturation of the tumor or hemorrhagic necrosis and distortion of the original neoplasm resulting in fibrous tissue. In the authors' experience not a single instance of ganglioneuroma becoming neuroblastoma has occurred.

Relative to treatment it is pointed out that caution should be employed in excision of ganglioneuromas which are intimately bound to vital structures since long term follow-up suggests that such tumors partially excised do not cause further symptoms.—Lionel W. Young, M.D.

ELIASON, ORLAND, and DUNLAP, DAVID. Osteomyelitis of the spine following needle biopsy of the prostate. J. Urol., Sept., 1965, 94, 271-275. (From: Veterans Administration Hospital, Minneapolis, Minn.)

Urinary tract infection and subsequent osteomyelitis of the spine has been reported in many cases following surgery on the lower urinary tract. The incidence of clinically recognized osteomyelitis of the vertebrae following needle biopsy is low but the true incidence may be greater than is presently suspected.

The authors report 2 instances of overt osteomyelitis occurring in the lumbar vertebrae, each of which followed perineal biopsy of the prostate gland. There is presumptive evidence that the infection was transmitted through the vertebral circulation of Batson.

The 4 phases in the development of osteomyelitis of the spine are: (1) a focus of infection in the lower urinary tract; (2) bacteremia with associated febrile reaction; (3) pain usually worse at night and occurring several weeks after the surgical manipulation; and (4) roentgenographic evidence of destruction of an intervertebral disk and adjacent vertebral bodies.

The roentgenographic evidence may occur 4 to 5 weeks after the onset of symptoms. In the early stage, it may be difficult to differentiate osteomyelitis from Pott's disease of the spine, but its response to antibiotics and immobilization are fairly prompt and indicates a nontuberculous infection. In some instances, organisms have been recovered from the vertebrae which are similar to the infecting organisms of the urinary tract.

Extension of the process may involve the spinal canal or more distant areas of soft tissue or bone.

The authors recommend pre- and postoperative antibiotic therapy as a prophylactic measure for this group of patients.—George W. Chamberlin, M.D.

SKELETAL SYSTEM

Delahaye, R. P., Mangin, H., Seris, H., and Schickelé, J. Les aspects radiologiques des lésions vertébrales du pilote "éjecté." (Radiologic aspects of the vertebral lesions of the ejected pilot.) J. de radiol., d'électrol. et de méd. nucléaire, Aug.-Sept., 1965, 46, 427-436. (From: Service d'Electroradiologie de l'Hôpital militaire d'Instruction Dominique-Larrey, à Versailles; Centre d'Enseignement et de Recherches de Médecine aéronautique à Paris; et Laboratoire de Médecine aérospatiale du Centre d'essais en vol de Brétigny-sur-Orge, France.)

The progress obtained in aviation has had its accompanying medical problems. In this presentation the authors are primarily concerned with vertebral lesions and injuries of the ejected pilot.

With the increased speed of the airplane, the ejectable seat has been devised for the purpose of preventing the pilot from colliding with the posterior part (back or rear) of the airplane. As the seat is separated from the plane, it develops a speed of at least 17 to 18 meters per second.

The process of ejection occurs in four stages:

- (1) the preparation for ejection, during which the pilot assumes a position which should avoid or prevent flexion of the vertebral column
- (2) the actual ejection
- (3) abandonment of the seat, previously at the pilot's command, but now automatic

(4) parachuting and landing, the opening of the parachute being automatic

Fracture of the vertebral column, the primary medical problem of ejection, occurs either during ejection or landing.

Fractures incurred by the pilots may be asymptomatic and escape clinical manifestation or may have definite clinical symptoms. The former can only be detected by routine roentgenographic examination of the spine of all ejected pilots.

Fractures with clinical manifestations may present neurologic signs with involvement of the central nervous system; particularly, hemiplegia. The majority of cases, however, present symptoms of dorsal or lumbar pain. This was observed in 11 out of 13 cases.

In 2 cases of asymptomatic fractures, the discovery of the fracture was due to the compulsory routine roentgenologic examination required by the French Air Force.

The roentgenologic examination shows the extent, location, and degree of the injury.

A radiodynamic study often reveals the extent of mobility or limitation of motion, changes in the width of the intervertebral spaces, and the integrity of the ligaments, demonstrated by roentgenograms made in anteroposterior as well as lateral flexion and extension. The fractures may involve the vertebral body to the exclusion of the posterior wall, or may include the posterior wall—designated as stable and unstable fractures, respectively.

Of the 17 cases studied, 16 presented an intact posterior wall (stable fractures) while 1 case presented a fracture of the posterior wall involving D8 (unstable fracture).

Fractures of the body without involvement of the posterior wall are compression fractures with varying degrees of deformity. There may be concomitant involvement of the intervertebral disk and adjacent ligaments.

In I case of fracture with involvement of the posterior wall there was central compression and fragmentation, with bipartition of the vertebral body. However, the over-all height was not appreciably altered.

The radiologic examination should include routine roentgenograms in the lateral and frontal projections spot roentgenograms, and tomograms.

Fractures due to ejection are compression fractures occurring with the vertebral column in flexion. These are located in the dorso-lumbar area. However, if the vertebral column is in hyperflexion, the fracture may involve the posterior wall.

Ten figures, representing reproductions of roentgenograms, diagrams, and sketches, accompany this interesting article.—William H. Shehadi, M.D.

FAHEY, JOHN J., and O'BRIEN, EUGENE T. Acute slipped capital femoral epiphysis: review of the literature and report of ten cases.

J. Bone & Joint Surg., Sept., 1965, 47-A, 1105-1127. (Address: Dr. Fahey, 1791 West Howard Street, Chicago 26, Ill.)

Acute slipping is defined as an abrupt displacement of the capital epiphysis superimposed on pre-existing epiphyseolysis. The patients complain of severe pain. There is limited motion, external rotation, shortening and inability to bear weight. The literature on 75 acute slipped epiphyses is reviewed. In these cases, 2 year follow-ups showed 48 per cent satisfactory results in 40 cases with closed reduction and cast, 65 per cent in 23 cases of closed reduction and internal fixation, and 83 per cent satisfactory results in 12 cases with open reduction.

The authors had 10 cases, all with acute symptoms of 3 weeks' duration or less superimposed on prodromal symptoms. Two of these patients had no known injury. They were treated with gentle manipulation under anesthesia; 9 patients had 2 or 3 partially threaded pins inserted and 1 had a spica cast. Crutch walking without weight bearing was started between 2 and 3 weeks after operation and partial weight bearing in 3 to 4 months was allowed in all but the patient immobilized in the cast. These 10 cases are reported in detail and their roentgenograms reproduced. Good results were obtained in the 9 cases fixed with pins. In the patient placed in the spica, the femoral head showed flattening with cystic changes at 24 years, but function was good.

The authors emphasize the good results obtained with early diagnosis and fixation in situ. They prefer partially threaded pins rather than a Smith-Petersen nail, because the nail may cause distraction or spinning of the head during insertion so that avascular changes may result. There is also a danger of a late subtrochanteric femoral fracture at the site of nail insertion. Closed reduction should be avoided if more than 2-3 weeks have elapsed since the acute episode.

The authors state that in the absence of radiologic evidence of joint narrowing, aseptic necrosis, or marginal spurring on the head 2 to 3 years postoperatively, a long term favorable outcome can be expected. They recommend reduction by early manipulation and extra-articular fixation with 2-3 pins in acute slipped capital femoral epiphyses.—Martha Mottram, M.D.

WILSON, PHILIP D., JACOBS, BERNARD, and SCHECTER, LAURENCE. Slipped capital femoral epiphysis: an end-result study. J. Bone & Joint Surg., Sept., 1965, 47-A, 1128-1145. (From: Hospital for Special Surgery—affiliated with the New York Hospital-Cornell Medical Center, New York, N. Y.)

The authors present the end results obtained in 240 patients with 300 slipped capital femoral epiphyses. Twenty-six per cent had a history of preceding trauma; 28 per cent had bilateral involvement. There

were 142 cases with slight slipping (less than one-third the diameter of the neck in any plane), 76 with moderate slipping, (one-third—one-half shift), and 82 with severe slipping (displacement of greater than one-half the diameter of the neck). There was a 13 week interval between first symptoms and diagnosis in the patients with slight slipping and 28 weeks in the cases with severe slipping. Diagnostic errors resulted in delay in therapy in 77 patients (26 per cent); 48 per cent of these had moderate or severe slipping.

In half the cases, pain was referred to an area some distance from the hip—knee or lower thigh. There was limping, abnormal position and restricted motion in most cases. In unilateral involvement the left hip showed slipping in 108 patients, and the right in 72; bilateral slipping was diagnosed simultaneously in 29 patients. An interval of 6 weeks to 48 months was present in the other patients before slipping of the

opposite epiphysis occurred.

The patients are divided into two categories. The first includes those treated by fixation with acceptance of the deformity, and the second those treated by correction of the deformity and fixation. The operative procedures varied with the many surgeons, but comprise 55 wedge osteotomies of the neck, 9 trochanteric osteotomies, 6 osteoplasties of the femoral neck and 13 open or closed reductions; 203 hips had a Smith-Petersen nailing and 7 multiple pins.

In the first group of 187 hips with fixation in situ, 9 per cent showed fair or poor clinical results and 13 per cent fair or poor roentgenographic results. In this group there were 127 with slight slipping, 56 with moderate and 4 with severe slipping. The 5 poor results were each associated with a definite complication; in 4, epiphyseal distraction occurred during fixation with subsequent osteoarthritis and 1 had infection.

In the second group of 76 hips with correction of the deformity 38 per cent had fair or poor clinical results and 45 per cent fair or poor roentgenographic results. In this group there were no cases of slight slipping, 17 had moderate slipping, and 56 severe slipping. Seven of the poor results were associated with surgical complications: 5 epiphyseal distractions, I inadequate fixation and I wound infection. In each case of distraction a Smith-Petersen nail had been used. Subtrochanteric fracture occurred in 6 hips just distal to the outer end of the nail. Twentyseven cases showed intra-articular intrusion of the fixation device; this did not appear to influence the end result in any case, and 23 had good clinical and roentgenographic results. Three cases had premature extrusion of the fixation device.

Spinning of the head occurred in 3 hips with eventual poor clinical and roentgenographic results. Multiple drives of the nail across the epiphyseal plate did not induce epiphyseal distraction or aseptic necrosis. Epiphyseal closure occurred from 3 months to 3 years

after treatment, with an average of 9 months. Avascular necrosis occurred in 5 hips in the second group. Acute cartilaginous necrosis with rapid narrowing of the joint space and ankylosis occurred in 12 hips. Osteoarthritis developed at a later date and was slower in its evolution than bone or cartilaginous necrosis.

The literature for various procedures is reviewed. The authors reserve closed reduction for acute marked slipping. In their hands fixation in situ with multiple small partially threaded pins or a modified Smith-Petersen nail is the procedure of choice as it prevents further slipping, does not affect limb growth and permits rapid return to full weight bearing.—

Martha Mottram, M.D.

LAURENSON, RAE DUNCAN. Development of the acetabular roof in the fetal hip: an arthrographic and histological study. J. Bone & Joint Surgery, July, 1965, 47-A, 975-983. (From: Department of Anatomy, University of Alberta, Edmonton, Alberta, Canada.)

Fourteen fetuses, free of abnormalities, were studied using arthrographic and histologic methods. The fetal age ranged from 14 weeks to full term. After sufficient soft tissue had been removed from the area of the hip joint to expose the capsule, a small amount of contrast material was injected into each joint and roentgenograms were made. Histologic sections were then cut in the same plane as the roentgenograms.

In the 14 week old fetus, the acetabular roof was entirely cartilaginous and a well formed limbus was evident laterally. The zona orbicularis fitted closely around the neck of the femur. The ligamentum teres was evident and there was evidence of an acetabular fossa and of a transverse ligament of the acetabulum.

All the features noted in the 14 week old fetus were increasingly conspicuous in the older fetuses.

The arthrographic criteria of a normal hip joint are enumerated; these criteria were fulfilled even in the youngest fetus in the series. The acetabulum covered the femoral head to a considerable degree from 14 weeks to birth.

Ossification of the acetabular roof is discussed. The bony roof was found to consist of central endochondral bone and lateral and medial sheets of perichondral bone. The development of the medial sheet of perichondral bone precedes the lateral sheet, and it is suggested that pressure from a displaced femoral head upon the limbus and lateral spur causes retardation of perichondral ossification. Hence, endochondral ossification in the lateral part of the acetabular roof is also delayed.—David M. Rankin, M.D.

Kelly, Patrick J., Martin, William J., and Coventry, Mark B. Bacterial arthritis of the hip in the adult. J. Bone & Joint Surg., July, 1965, 47-A, 1005-1018. (From Section of Orthopaedic Surgery and Section of Medicine, Mayo Clinic and the Mayo Foundation, Rochester, Minn.)

A retrospective study of 26 adult cases of bacterial arthritis observed from 1942 through 1962 was made with the following results:

Staphylococcus aureus caused over 60 per cent of the infections, and was blood borne in almost all cases (cases of brucellar, tuberculous, fungal, and gonococcal infection were excluded from this study).

Predisposing factors included focal infections such as diabetic skin ulcers, appendicitis, etc. Prior abdominal or urogenital procedures and intra-articular injections preceded some cases.

Diagnostic aids comprised hip arthralgia, fever, elevated erythrocyte sedimentation rate and a leukocytic response. Roentgenographic findings of early hip osteoporosis and slight narrowing of the joint space, later followed by bone destruction, were noted. Capsular distention was not clearly seen in adults.

Adult hip infection is best treated by combined antimicrobial drugs and surgical procedures. Accurate bacteriologic identification and *in vitro* sensitivity tests help in the choice of drugs. Bacteriocidal regimen is preferred and *Penicillin G* remains the drug of choice for staphylococcus. Open drainage and spica immobilization of the hip are recommended followed by formal debridement if the infection persists.

Disability of the patients was severe and prolonged with only one-third regaining pre-infection activity and 12 per cent pre-infection function.

Although desirable, spontaneous ankyloses were not observed in those with only staphylococcal infection. It was observed in 2 patients with rheumatoid disease and bacterial arthritis:—Donald C. Moore, M.D.





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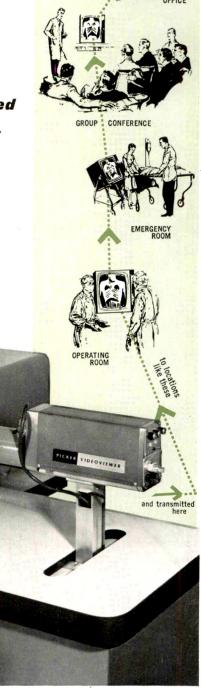
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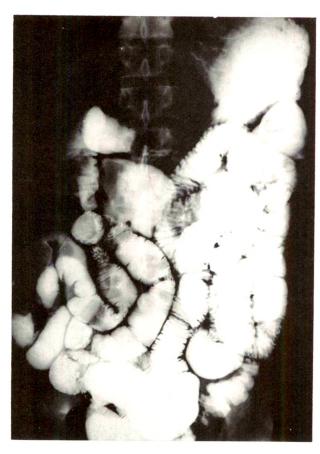
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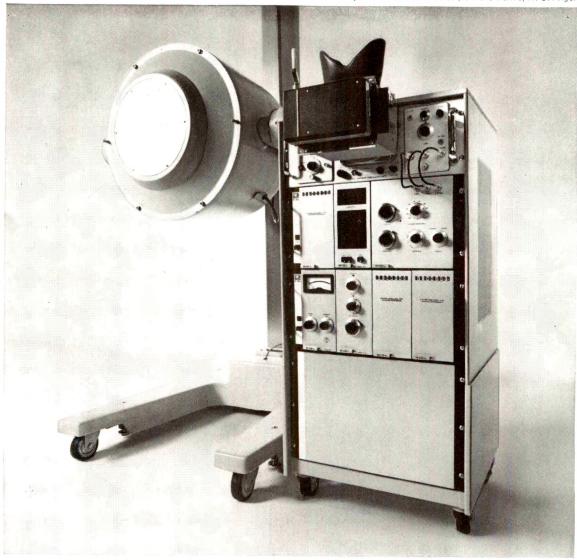
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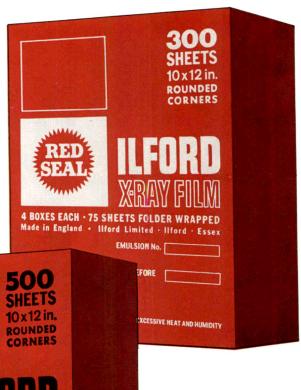
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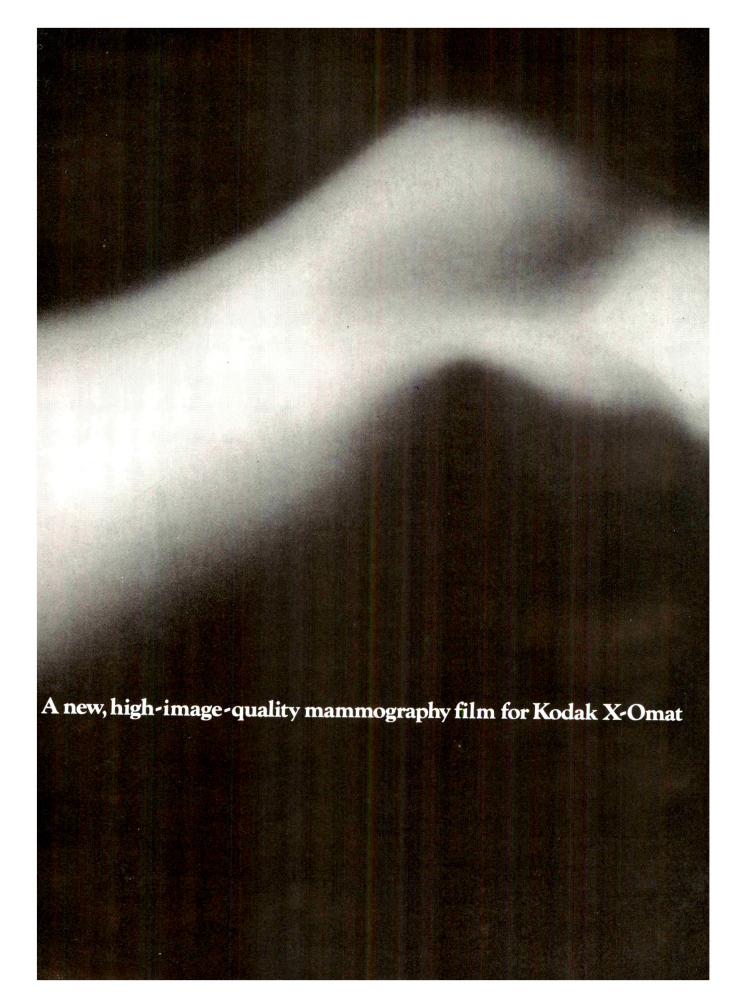
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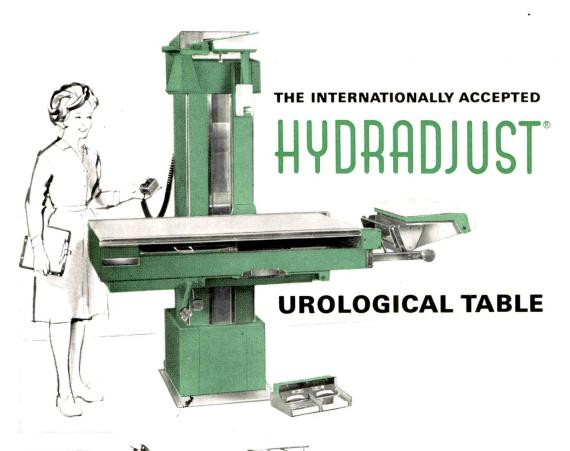
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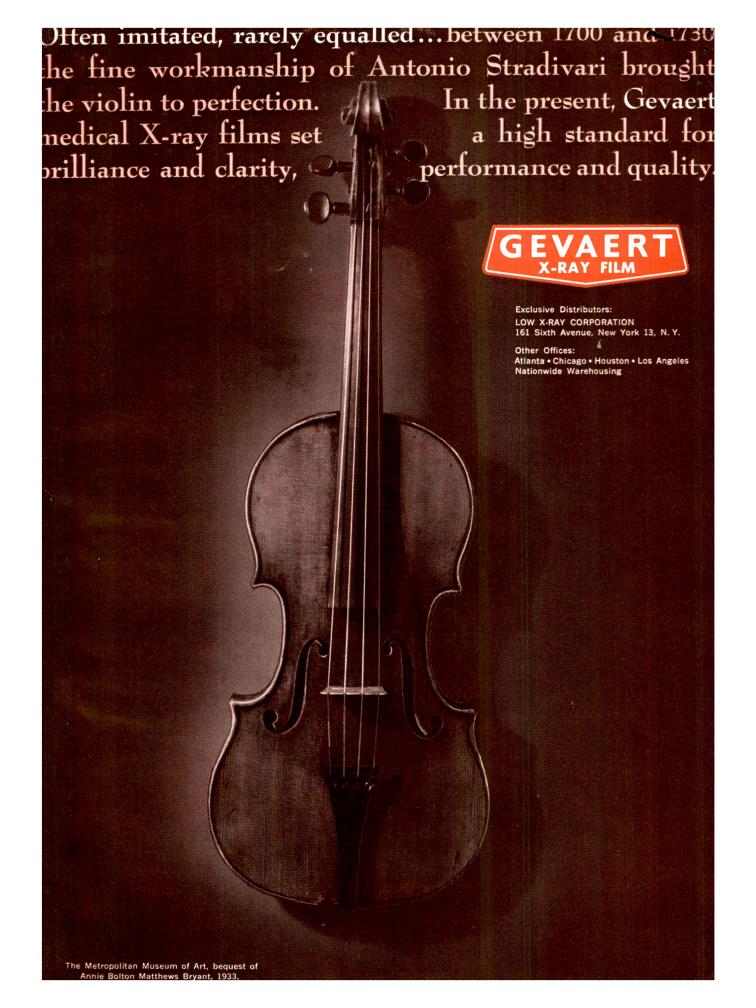


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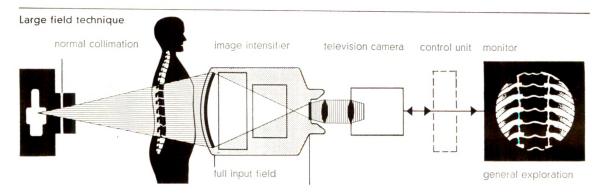


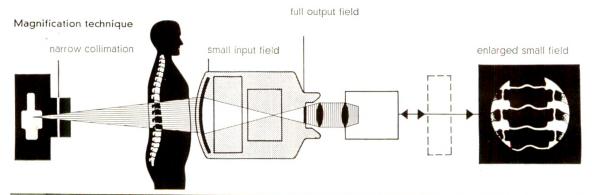


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